gave 72 mg of a red solid with mp and ^{1}H NMR properties identical with those of quinone **13**. The ^{13}C NMR spectrum indicated that ^{18}O had been incorporated on C-4 and the CIMS data indicated that the product consisted of 68% of ^{18}O-labeled quinone **14** and 32% of unlabeled quinone **13**: ^{13}C NMR (Me$_2$SO-d_6) δ 14.60 (CH$_3$), 25.73 (CH_2CH$_2$N), 38.56 (CH$_2$N), 59.37 (OCH$_2$), 106.31 (C-6), 119.43 (C-3), 122.65 (C-2), 123.15 (C-3a), 132.05 (C-7a), 156.11 (CO$_2$), 159.47 (C-5), 178.50 (C-7), 178.70 (C-4 of **14**, rel intensity 41.6), 178.75 (C-4 of **13**, rel intensity 28.8); CIMS *m/e* (rel intensity) 279 (51.9 MH$^+$), 281 (100.0), 282 (17.2).

Oxidation of 12 with O$_2$ in H$_2$^{18}O. To a stirred mixture of **12** (27 mg, 0.1 mmol), NaHCO$_3$ (38 mg, 0.45 mmol), and CH$_3$CN (2.5 mL) under an atmosphere of dry air (volume of air above solution was 60 mL) was added H$_2$^{18}O (1 g, containing 50 atom % ^{18}O) and the stoppered reaction mixture was stirred at 25 °C for 24 h. Workup as described above gave 16 mg of a red solid with melting point and ^{1}H NMR properties identical with those of quinone **13**: CIMS *m/e* (rel intensity) 279 (100.0, MH$^+$), 280 (15.5), 281 (18.8). Comparison of these MS data with those of pure **13** indicated formation of **13** and ^{18}O-labeled **13** in a ratio of 87.7:12.3 (or in a ratio of 75:25 based on H$_2$^{18}O containing 100 atom % ^{18}O).

Treatment of 13 with H$_2$^{18}O. To a mixture of **13** (14 mg, 0.05 mmol), NaHCO$_3$ (19 mg, 0.23 mmol), and CH$_3$CN (2.5 mL) under an Ar atmosphere was added H$_2$^{18}O (1 g, containing 50 atom % ^{18}O) and the stoppered reaction mixture was stirred at 25 °C for 24 h. Workup as described above for the isolation of **13** gave 10 mg of a red solid with melting point and ^{1}H NMR properties identical with those of quinone **13**: CIMS *m/e* (rel intensity) 279 (100, MH$^+$), 180 (17.5), 281 (18.6). Comparison of these MS data with those of pure **13** indicated formation of **13** and ^{18}O-labeled **13** in a ratio of 87.9:12.1 (or in a ratio of 76:24 based on H$_2$^{18}O containing 100 atom % ^{18}O).

Acknowledgment. The support of this work through a grant from the National Institute of Neurological and Communicative Disorders and Stroke (NS15692) is gratefully acknowledged.

Kinetics and Mechanism of the Bromination of Phenols and Phenoxide Ions in Aqueous Solution. Diffusion-Controlled Rates[1]

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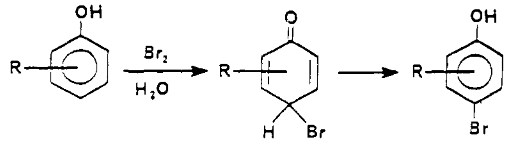
Abstract: Second-order rate constants (k_2^{obsd}) for the aqueous bromination of various phenols, pyridones, and pyrimidones have been measured in the pH range 0–7. For phenols the acidity dependence follows: $k_2^{\text{obsd}} = k_2 + k_2'K_a/[\text{H}^+]$, where k_2 is for bromine attack on the phenol, k_2' is for the phenoxide ion, and K_a is the phenol acid dissociation constant. Values of k_2 vary widely and systematically ($\rho^+ = -5.2$ for *p*-substituted phenols), but for 16 phenoxide ions the values of k_2' are nearly constant: $(1\text{–}9) \times 10^9$ M^{-1} s^{-1}, at or close to the diffusion-controlled limit. Strong electron withdrawal ($\sigma^+ > 0.9$) is necessary to lower k_2' much below this limit. Since the k_2' values hardly vary, the contribution of the anion route is determined largely by the phenol acidity. The facile tribromination of phenol arises since the mono- and dibromophenols are more reactive than phenol at intermediate pHs. Tribromide ion reacts with phenoxide ion at almost the same rate as Br$_2$, but its reaction with phenol is insignificant. The mechanism of bromination of phenols via cyclohexadienones is discussed; it appears that the protonated dienone is not a mandatory intermediate. Values of ρ^+ for the bromination of monosubstituted benzenes in water, CF$_3$COOH, and in CH$_3$COOH are virtually the same, suggesting that solvent stabilization of the Wheland intermediate is not of primary importance.

Phenols react readily with bromine to undergo electrophilic substitution at positions ortho and para to the hydroxyl group.[2] These reactions proceed via cyclohexadienone intermediates,[3,4] and recent studies in this laboratory have shown that transient 4-bromo-2,5-cyclohexadienones can be observed during the bromination of phenol and alkyl derivatives (eq 1) (and 1-naphthols) in aqueous solution.[5]



(1)

In aqueous solution the bromination of phenol proceeds rapidly,[6] and with sufficient bromine it leads quickly to the formation of 2,4,6-tribromophenol.[7] In fact, controlled mono- or dibromination of phenol is difficult to achieve. Among other things, the present work provides insight into the course of the tribromination and shows how the reaction can be controlled.

There have been few previous kinetic studies of the bromination of simple phenols in aqueous solution, presumably because the reactions are so fast that special techniques are required. Bell and Rawlinson[6] studied six phenols in dilute aqueous perchloric acid by using a potentiometric method. They showed that bromine reacts with the phenol or its anion, depending upon the pH. Phenoxide ions bearing only one electron-withdrawing substituent react with bromine at or near the diffusion-controlled limit,[8] and for some of these anions a small amount of reaction was attributed

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(1) Based upon studies reported in: (a) Paventi, M. Ph.D. Thesis, Concordia University, Montréal, 1984. (b) Bennett, J. M. M.Sc. Thesis, Concordia University, Montréal, 1986.

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(6) Bell, R. P.; Rawlinson, D. J. *J. Chem. Soc.* **1961**, 63. Rate constants were extrapolated to zero ionic strength.

(7) Mann, F. G.; Saunders, B. C. *Practical Organic Chemistry*, 3rd ed.; Longmans, Green, and Co.: London, England, 1957.

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Table I. Rate Constants for the Bromination of Phenol and Bromo Derivatives in Aqueous Solution[a]

phenol	pK_a	k_2, M^{-1} s^{-1}	k_2', M^{-1} s^{-1}
parent	10.00	4.1×10^5	2.4×10^{10}
2-bromo	8.44	1.5×10^4	1.7×10^{10}
4-bromo	9.36	4400[b]	1.5×10^{10}
2,4-dibromo	7.79	~300	3.7×10^9
2,6-dibromo	6.67	~500	2.7×10^9
2,4,6-tribromo	5.93[d]		~1700[c]

[a] At 25 °C, in 1.0 M KBr, pK_as are taken from: Biggs, A.; Robinson, R. A. *J. Chem. Soc.* **1961**, 388. Robinson, R. A. *J. Res. Nat. Bur. Stand., A. Phys. Chem.* **1967**, *71*, 213. The values of k_2' for first three entries are elevated due to polybromination and/or reaction with Br_3^- (see text). Based on the data in Table S1. [b] Note that the value of $k_2 = 3.2 \times 10^9$ M^{-1} s^{-1} which is given in ref 6 is a typographical error; it should have been 3200 M^{-1} s^{-1} (Bell, R. P., personal communication). Unfortunately, the erroneous value has appeared in several reviews and compilations. [c] Based on measurements at one pH (see text). [d] This work.

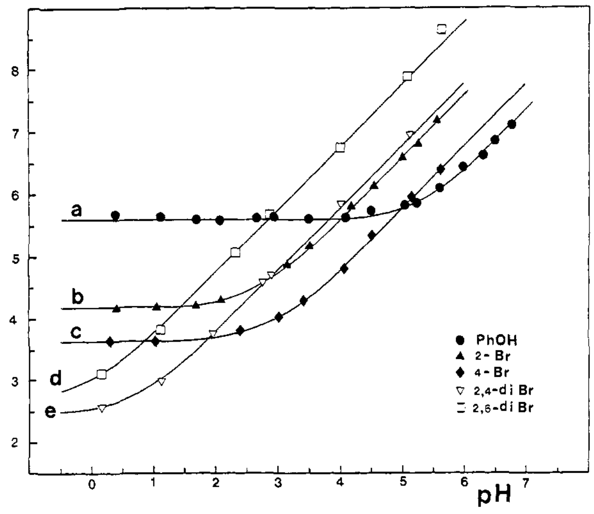

Figure 1. pH-rate profiles for the bromine attack on phenol and bromo derivatives in 1.0 M aqueous KBr (a) phenol, (b) 2-bromophenol, (c) 4-bromophenol, (d) 2,6-dibromophenol, and (e) 2,4-dibromophenol, from the data in Table S1. The derived rate constants (k_2 and k_2') are collected in Table I.

Table II. Rate Constants for the Bromination of Substituted Phenols and Phenoxide Ions in Aqueous Solution[a]

phenol	pK_a	k_2, M^{-1} s^{-1}	k_2', M^{-1} s^{-1}	note/ref
parent	10.00	4.3×10^5	~1.2×10^9	*b*, *c*
2-Me[d]		1.5×10^6		12c
2-COO^-[e]		3.3×10^6		12b
2-Br	8.31[f]	1.0×10^4	6.2×10^9	12c
2-COOH		4700		12b
2-COOMe	9.87[g]	610	7.2×10^9	12b
2-NO_2	7.12[f]	<100	1.7×10^9	*b*
3-NO_2	8.24[f]	~110	2.7×10^9	*b*
4-Me		6.6×10^3		12c
4-*t*-Bu		5.9×10^5		12c
4-COO^-	9.31[h]	(2.6×10^6)[i]	3.5×10^9	12a
4-Br[j]	9.36	3900[k]	5.5×10^9	12c
4-COOH	(8.30)[l]	3500	8.2×10^9	12a
4-COOEt	8.39[f]	2200	6.4×10^9[m]	12a
4-CN	7.84[f]	155	2.6×10^9	*b*
4-NO_2	7.03[f]	<60	1.2×10^9	*b*
2,4-diMe[d]		3.0×10^6		*b*
2,6-diMe[d]		2.0×10^6		*b*

[a] At 25 °C, $I = 0.11$ M (KBr + buffer). Values of k_2 and k_2' may differ from Table I because of the different media used, and because corrections have been made for dibromination or reaction with tribromide ion. pK_a values are as in Table I (parent,4-Br) or from the sources cited. Only the k_2' value for the parent has been corrected for reaction with Br_3^-. Such reaction was not found for nitrophenoxide ions (in 0.1 M KBr); it is believed to be unimportant for other "deactivated" anions, also. With one exception (4-Br) no correction was made for dibromination. It is not important for 4-COOH.[12a] [b] This work, from the data in Table S2. [c] Value of k_2' is based on the intercept of the line[18] in Figure 3 (see text). [d] In 1.0 M KBr. [e] Salicylate ions show enhanced reactivity.[12b] [f] From the thermodynamic value (Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology*, 3rd ed.; Fassman, G. D., Ed.; CRC Press: Cleveland, OH, 1976; Vol. 1, p 314) and a correction of -0.11 for $I = 0.1$ M (Perrin, D. D.; Dempsey, B. *Buffers for pH on Metal Ion Control*; Chapman and Hall: London, U.K., 1974; Table 2.3, p 20). [g] Perrin, D. D. *Nature (London)* **1958**, *182*, 741. [h] Kortum, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* **1961**, *1*, 190. [i] This value is only "apparent" since the 4-hydroxybenzoate ion reacts as 4-carboxyphenoxide ion.[12a] [j] Value of k_2' has been divided by 2 to account for dibromination (see text). [k] See footnote *b* of Table I. [l] Estimated from a Hammett plot for the ionization of phenols.[12a] [m] Differs from the literature value[12a] because of the correction to the pK_a for ionic strength (see footnote *f*).

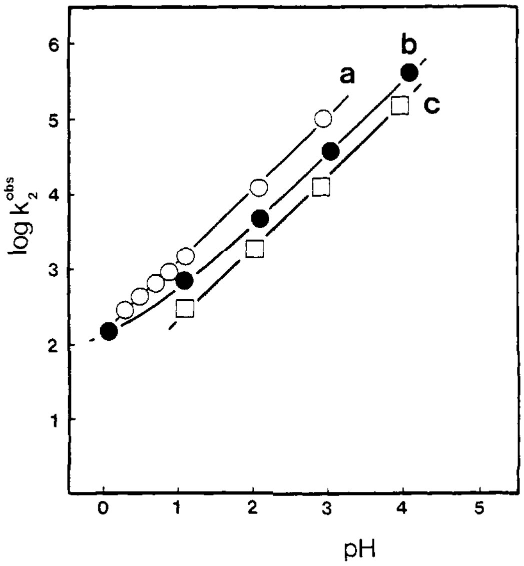

Figure 2. pH-rate profiles for the bromination of (a) 4-nitrophenol, (b) 4-cyanophenol, and (c) 3-nitrophenol, from the data in Table S2. The profile for 2-nitrophenol is virtually coincident with that of its 4-isomer.

to attack by tribromide ion. An approximate rate constant was obtained for the attack of bromine or phenol itself, but no reaction of phenoxide ion was detected at the acidities used.[6]

Subsequently, Kulic and Vecera used the stopped-flow method to study the bromination of five other phenols, also in dilute perchloric acid.[9] They estimated second-order rate constants from half-lives, and overall their results are similar to those of Bell and Rawlinson,[6] although probably less accurate.

We studied the bromination of pyrimidones,[10] pyridones,[11] and of bromopyridones[11] in aqueous solution. At certain pHs these substrates react via their anions, and, in order to correlate their rates with those of phenoxide ions, we measured rate constants which had not been determined previously. We have studied the bromination of phenol, 2-bromo-, 4-bromo-, 2,4-dibromo-, and 2,6-dibromophenol over as wide a range of pH as possible, as now reported here.

Prompted by this initial work, various other studies of the bromination of phenol derivatives were carried out, most of which have already been published.[5,12] In the present paper we report additional findings which have previously appeared only in theses.[1] In particular, the effect of substituents on the diffusion-controlled reactions is explored.

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(9) Kulic, J.; Vecera, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 71.

(10) (a) Tee, O. S.; Paventi, M. *J. Org. Chem.* **1980**, *45*, 2072. (b) Tee, O. S.; Paventi, M. *J. Org. Chem.* **1981**, *46*, 4172.

(11) (a) Tee, O. S.; Paventi, M. *J. Am. Chem. Soc.* **1982**, *104*, 4142. (b) Tee, O. S.; Paventi, M. *Can. J. Chem.* **1983**, *61*, 2556.

(12) (a) Tee, O. S.; Iyengar, N. R.; Kraus, B. *J. Org. Chem.* **1985**, *50*, 973. (b) Tee, O. S.; Iyengar, N. R. *J. Org. Chem.* **1985**, *50*, 4468. (c) Tee, O. S.; Bennett, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 269.

Results

Kinetics. As found in earlier work,[5,6,9,12] the reaction of phenol and its derivatives with aqueous bromine follows a second-order rate law: first-order in substrate and in bromine. For the most part, rates were measured as the first-order disappearance of bromine in the presence of an excess of the substrate, and the observed pseudo-first-order rate constants were converted to second-order constants (k_2^{obsd}), assuming that there is no reaction with tribromide ion.[13,14] In what follows it should be noted that the initial work (Figure 1 and Table I) used 1.0 M aqueous KBr as the basic medium, whereas most of the later studies (Figure 2 and Table II) employed 0.1 M KBr.[13] Reasons for using such high concentrations of bromide ion have been given previously.[14]

Phenol and Its Bromo Derivatives. Figure 1 shows pH log rate profiles for the attack of bromine on these derivatives, constructed from the data in Table S1 of the Supplementary Material. The values of k_2^{obsd} show little variation at low pH but increase in the manner appropriate for reaction of the phenoxide ions as the pH is raised. This acidity dependence may be expressed by

$$k_2^{\text{obsd}} = k_2 + k_2'K_a/[\text{H}^+] \tag{2}$$

where k_2 is the rate constant for reaction of the undissociated phenol, k_2' is that for the phenoxide ion, and K_a is the acid dissociation constant for the phenol. The curves drawn in Figure 1 were calculated from eq 2 by using the constants given in Table I.

For phenol k_2 is 4.1×10^5 M^{-1} s^{-1}, somewhat higher than the value of 1.8×10^5 M^{-1} s^{-1}, determined by Bell and Rawlinson, which was stated to be of low accuracy.[6] The rate constant for the reaction of phenoxide ion with bromine is very high (2.4×10^{10} M^{-1} s^{-1}) and seemingly above the diffusion-controlled limit.[8] This may be due to contributions from reaction with tribromide ion or polybromination; these possibilities are considered more explicitly, later.

For the bromophenols (Table I) the values of k_2 decrease when one and two bromines are introduced, as expected for electron-withdrawing substituents.[2] Thus, close to pH 0, where all of the substrates react with bromine as their undissociated forms, the pH-rate profiles in Figure 1 are arranged in the order that one anticipates. However, above pH 5, where all the phenols react as anions, the order of the profiles is reversed. This situation arises because the rate constants k_2' for the anions are very similar, whereas the dissociation constants K_a for the phenols increase substantially with each bromo substituent. As a consequence, the second term of eq 2 is larger for the more acidic bromophenols, and so their rate profiles rise above that for phenol (Figure 1). In practical terms this means that at intermediate pHs the mono- and dibromophenols are effectively more reactive than phenol toward bromine and that di- and tribromination are possible, even when phenol is in excess.[15]

Product Analysis. The proportions of *o*- and *p*-bromophenols arising in the bromination of phenol were determined by quantitative GC measurements. At pH 1, where phenol is more reactive than its bromo derivatives (Figure 1), there is predominant monobromination, and the product ratio corresponds to 82% para and 18% ortho attack. At pH 7.5, where all of the substances in Table I react via their anions (Figure 1), the para/ortho ratio is 58/42. This ratio is probably distorted by preferential consumption of the *o*-bromophenol since 82% of the bromine is converted to 2,4,6-tribromophenol. Above pH 10, where all of the phenols are ionized and react at 10^9–10^{10} M^{-1} s^{-1}, there is a lesser amount of tribromination (16%), and the attack on phenoxide ion appears to be virtually statistical: 68% ortho and 32% para. These relative proportions of ortho and para products were basically the same whether the initial ratio of phenol/bromine was 10:1 or 1:1. However, with a 1:1 ratio of reactants more polybromination was apparent at the higher pHs, as one would expect.

Table III. Rate Constants for the Bromination of Pyridones, Pyrimidones, and Their Anions[a]

substrate	pK_a	k_2, M^{-1} s^{-1}	k_2', M^{-1} s^{-1}	note/ref
2-pyridone	11.62	22000	5.0×10^9	11a
3-bromo	10.42	1600	6.0×10^8	11a
5-bromo	10.03	380	4.9×10^5	11a
4-pyridone	11.09	10000	1.4×10^9	11b
3-bromo	9.46	790	8.3×10^7	11b
2-pyrimidone	9.17	~250	4.8×10^7	*b*
4-pyrimidone	8.60	~11	1.2×10^7	*b*

[a] At 25 °C, $I = 0.11$ M (KBr + buffer). The pK_as are as in ref 10 and 11. [b] At 30 °C. Values of k_2 for the parents are approximate.[1a] Values of k_2' for the anions are based on the data in Table S3.

Substituted Phenols. We have also measured the pH dependences of the rates of bromination of many other phenols, mainly in 0.1 M aqueous KBr. The values of k_2 and k_2' which have been obtained are collected in Table II. Some of these constants originated in studies which have already been published,[12] but many are presented here for the first time, based on the pH-rate data in Table S2.

With the exception of those substrates which bear a carboxyl group,[12a,b] the rate profiles for substituted phenols may also be generated from eq 2. However, the relative importance of the two terms in that equation varies markedly with the substituent. As seen earlier in Figure 1, reaction of the phenoxide ion becomes progressively more important with increasing electron withdrawal by the substituent, due to the lowering of the phenol pK_a, so much so that with the nitrophenols reaction of their anions persists down to below pH 1 (see Figure 2).

As discussed later, the values of k_2 for the phenols in Table II vary in a regular manner with the electronic nature of the substituent. In contrast, the values of k_2' for the phenoxide ions vary little, and are all in the range 10^9–10^{10} M^{-1} s^{-1}. Admittedly, some of these may be elevated (by up to a factor of 2) due to dibromination or, less likely, due to some contribution from reaction with Br_3^- (see Discussion). In any event, the values of k_2' are all close to the diffusion-controlled limit.[8] This observation raises the question of how much electron withdrawal by substituents is required to bring k_2' down below this limit. Bell and Rawlinson[6] obtained rate constants for the 2,4- and 2,6-dinitrophenoxide ions (1.0×10^6 and 5.4×10^6 M^{-1} s^{-1}) which are lower; we have studied some heterocyclic substrates that provide additional, lower values.

Related Heterocycles. The anions of pyridones are phenoxides having an aza nitrogen (=N—) substituent.[16] Furthermore, as has been pointed out by others,[17] pyridones themselves can be considered as phenoxide ions bearing an azonium nitrogen (=NH$^+$—) as substituent.[16] Rate constants for the bromination of these substrates (and their bromo derivatives) are available from earlier work.[11]

Detailed studies have shown that below pH 5 both 2- and 4-pyrimidones react with bromine by way of covalent hydrates.[10] However, above pH 5 the reaction orders and pH dependences are consistent with reaction on the respective anions (Table S3). In the region of the changeover there is also evidence of some bromine attack on the parent pyrimidones.[1a]

Rate constants for the reaction of bromine with all these heterocyclic derivatives are collected in Table III.

Reaction with Tribromide Ion.[13] As mentioned above, one of the reasons for the high value of k_2' for phenoxide ion may be

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(13) For the dissociation constant of tribromide ion we have used 0.0625 M when $I = 1.0$ M (Jones, G.; Baeckstrom, S. *J. Am. Chem. Soc.* **1934**, *56*, 1517) and 0.0562 M when $I = 0.1$ M (Bell, R. P.; Ramsden, E. N. *J. Chem. Soc.* **1958**, 1294).

(14) Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830.

(15) This behavior must change again above pH 10 where all the phenols are completely ionized. Since the anions react with Br_2 at $\sim 10^{10}$ M^{-1} s^{-1}, polybromination is less likely if phenol is in excess (see Product Analysis). However, it should be noted that at high pH virtually all of the bromine will be in the form of HOBr and its anion,[11b,14] and so bromine may not be the active electrophile.

(16) Tomasik, P.; Johnson, C. D. *Adv. Heterocycl. Chem.* **1976**, *20*, 1.

(17) Bellingham, P.; Johnson, C. D.; Katritzky, A. R. *J. Chem. Soc. B* **1967**, *1226*. Acheson, R. M. *An Introduction to the Chemistry of Heterocyclic Compounds*, 2nd ed.; Interscience: New York, 1967; Chapter 5.

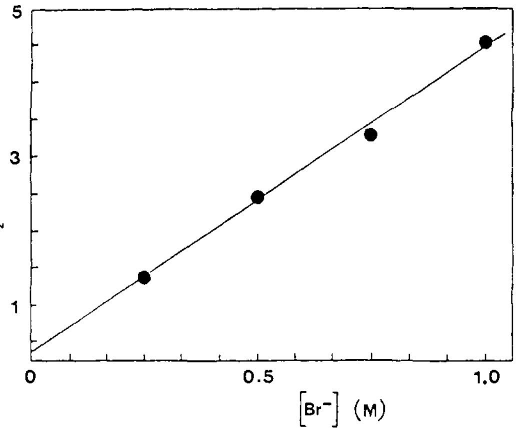

Figure 3. The linear dependence[18] of k_2^{obsd} on the bromide ion concentration for the bromination of phenol via its anion (at pH 6.48, I = 1.03 M = [KBr] + [KNO$_3$] + 0.03 M buffer salt). Data in Table S4.

a sizeable contribution to k_2^{obsd} from reaction with Br_3^-. If such a reaction is *not* involved, values of k_2^{obsd} (which are corrected for the formation of Br_3^-, HOBr, and OBr^-)[11b,14] should be invariant with [Br$^-$]. Such is not the case for phenol reacting via its anion (Table S4). As shown in Figure 3, values of k_2^{obsd} increase linearly[18] with [Br$^-$], consistent with a significant amount of attack by Br_3^- under the reaction conditions.

For reaction of a substrate with Br_2 (k_B) and Br_3^- (k_T) the apparent second-order rate constant is a weighted sum of the two contributions: $k_2^{app} = k_B f_B + k_T f_T$, where f_B is the fraction of total bromine existing free in solution and f_T is the fraction in the form of Br_3^-. In such cases the "observed" rate constant k_2^{obsd} should vary linearly with bromide ion concentration

$$k_2^{obsd} = k_2^{app}/f_B = k_B + k_T[Br^-]/K \qquad (3)$$

since $f_T/f_B = [Br^-]/K$, where K is the dissociation constant of Br_3^-. For phenol such linear dependence is observed (Figure 3), and from the slope and intercept of the line,[18] after correcting for the pH, we obtain a value of 1.2 × 10^9 M^{-1} s^{-1} for the attack of bromine on phenoxide ion and 8.5 × 10^8 M^{-1} s^{-1} for reaction with tribromide ion.[19] Thus, it appears that Br_3^- is almost as reactive as molecular bromine toward phenoxide ion.

In contrast to the case of phenol, values of k_2^{obsd} for 3-nitrophenol, reacting via its anion, were invariant with [Br$^-$] up to 0.1 M (Table S5).[20] Likewise, no effect of varying [Br$^-$] was found for 4-nitrophenol.[12c] Also, it should be noted that the values of k_2 which were obtained for phenol in 1.0 and 0.1 M KBr are virtually the same (Tables I and II), and so reaction between phenol and Br_3^- does not appear to be important.

Multiple Substitution. Clearly, polysubstitution may occur in the bromination of phenol at pH > 5 since the rate profiles for the mono- and dibromophenols rise above that of the parent (Figure 1). In consequence, the apparent second-order rate constants measured for phenol at such pHs may be elevated by as much as a factor of 3. Likewise, the rate constants obtained for 2- and 4-bromophenol at pH > 2 may be too large by a factor of 2. Obviously, the extent to which such distortions of the rate data occur depends upon the initial concentrations of the reactants and the various rate constants involved. As outlined in the Appendix, the situation may be clarified by carrying out experiments with stoichiometric amounts of the reactants and by analyzing the resulting rate data for second-order behavior. Rate constants obtained in this manner are presented in Table IV, together with values calculated from eq 2 and the appropriate parameters from Table I. The differences between the "observed" and "calculated" rate constants in Table IV are expressed by a "ratio" which is indicative of the extent of polybromination under the reaction conditions.

Table IV. Rate Constants for the Tribromination of Phenol and the Dibromination of 4-Bromophenol in Aqueous Solution[a,b]

phenol	pH	k_2^{obsd}, M^{-1} s^{-1}	k_2^{calcd}, M^{-1} s^{-1}	ratio
parent	5.29	5.60 × 10^5	8.78 × 10^5	1.6
	5.58	6.92 × 10^5	1.32 × 10^6	1.9
	6.10	2.35 × 10^6	3.43 × 10^6	1.5
	6.35	2.06 × 10^6	5.78 × 10^6	2.8
	7.08	1.11 × 10^7	2.93 × 10^7	2.6
	7.65	3.63 × 10^7	1.08 × 10^8	3.0
4-bromo	2.87	7.67 × 10^3	9.25 × 10^3	1.2
	3.50	1.60 × 10^4	2.51 × 10^4	1.6
	4.05	3.56 × 10^4	7.79 × 10^4	2.2
	4.95	2.92 × 10^5	5.88 × 10^5	2.0
	5.08	3.52 × 10^5	7.92 × 10^5	2.3

[a] At 25 °C, in 1.0 M KBr. Initial conditions: 3 × [phenol]$_0$ = [Br$_2$]$_0$ = 0.05 mM; 2 × [4-bromophenol]$_0$ = [Br$_2$]$_0$ = 0.0125, 0.025, or 0.05 mM. Values of k_2^{obsd} were obtained from an analysis in terms of $1/[Br_2] = 1/[Br_2]_0 + k_2 t$ (see the arguments given in the Appendix). The "k_2^{calcd}" were calculated from eq 2, and the parameters in Table I and "ratio" = k_2^{obsd}/k_2^{calcd}.

For phenol reacting with 3 equiv of bromine at pH > 5 the values of k_2^{obsd} which were found are 2–3 times lower than those calculated (Table IV). Therefore, di- and tribromination *do* contribute to the high value of k_2' for phenoxide ion in Table I. Similarly, for the reaction of 4-bromophenol with 2 equiv of bromine at pH > 2 the k_2^{obsd} values are about half those calculated from the parameters in Table I, indicating that the k_2' value for *p*-bromophenoxide ion is enlarged due to dibromination.

It has long been known that 2,4,6-tribromophenol reacts with bromine to give 2,4,4,6-tetrabromo-2,5-cyclohexadienone.[21] However, the rate of this reaction was found to be relatively slow (k_2^{obsd} = 567 M^{-1} s^{-1} at pH 5.62), and so it does not interfere with the measurement of the rate constants shown in Figure 1. Assuming that reaction takes place on the anion of 2,4,6-tribromophenol (pK_a = 5.93), the value of k_2' for that anion is 1700 M^{-1} s^{-1}.

Discussion

In general, the pH dependence of the rate of bromination of phenols may be expressed by eq 2[22] in which the two terms correspond to reaction of the phenol (k_2) and its anion (k_2'). Obviously, the contributions of the two pathways depend not only on pH but also on k_2, k_2', and on the pK_a of the phenol. As discussed below, the values of k_2 vary markedly with substituent, whereas for monosubstituted phenols, at least, the values of k_2' are almost constant and at the diffusion-controlled limit.[8] In consequence, the contribution of the anionic route is primarily determined by the phenol pK_a, and it becomes increasingly important for more acidic phenols. Thus, for nitrophenols reaction of the undissociated phenol, which is quite slow (k_2 < 120 M^{-1} s^{-1}), is barely detectable[23] in the normal range of pH (Figure 2).

Tribromide Ion. This species, which is generally a weak electrophile toward aromatic substrates,[2] reacts rapidly with phenoxide ion (8.5 × 10^8 M^{-1} s^{-1}), at almost the same rate as bromine (~1.2

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[18] Intercept = 0.355 (s.d. = 0.212) × 10^6 M^{-1} s^{-1}, slope = 4.11 (s.d. = 0.14) × 10^6 M^{-2} s^{-1}, r = 0.9973. Note that the intercept is not particularly accurate, given its standard deviation.

[19] From these values the apparent value of k_2' for reaction of phenoxide ion with bromine is 1.5 × 10^{10} M^{-1} s^{-1}, if all of the reaction is attributed to bromine. This agrees tolerably well with the value of 2.4 × 10^{10} M^{-1} s^{-1} (Table I) which was obtained from the data in Figure 1, given that this value is also elevated by polybromination (see later).

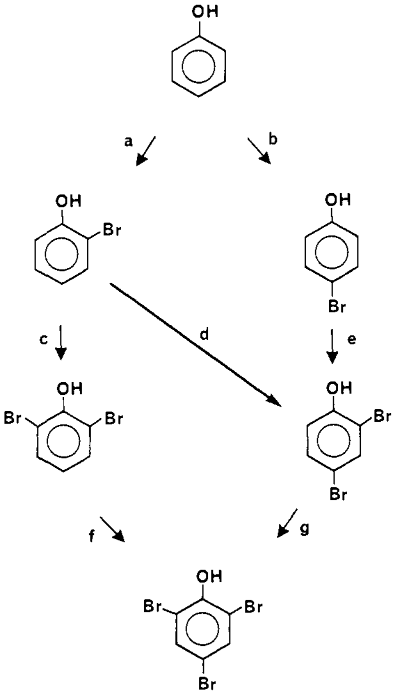
[20] Bell and Rawlinson[6] report a value of 2.8 × 10^7 M^{-1} s^{-1} for the reaction of Br_3^- with 3-nitrophenoxide ion, based on data with considerable scatter for [Br$^-$] up to 0.2 M. Under the present conditions ([Br$^-$] ≤ 0.1 M) reaction with such a rate constant would barely be detectable.

[21] Benedikt, R. *Justus Liebigs Ann. Chem.* **1879**, *199*, 127. Price, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 5436. Calo, V.; Cimanale, F.; Lopez, L.; Todesco, P. E. *J. Chem. Soc. C* **1971**, 3652.

[22] More complex expressions must be employed for phenols, such as salicylic acids[12b] and *p*-hydroxybenzoic acids,[12a] which possess an additional ionizable group.

[23] A value of k_2 = 110 M^{-1} s^{-1} for *p*-nitrophenol was obtained by Kulic and Vecera[9] from half-lives measured in dilute aqueous HClO$_4$. Our data suggest a lower value (Table S2, Table II, and Figure 2).

Scheme I



× 10^9 M^{-1} s^{-1}). Direct comparison of these rate constants may not be meaningful since they are so very close to the diffusion-controlled limit.[8] However, we note that Kresge and co-workers[24] have recently reported higher values for the attack of Br_3^- and Br_2 on the anion of malononitrile (3.8 × 10^9 and 8.3 × 10^9 M^{-1} s^{-1}, respectively). They concluded that the reactions of both bromine species are diffusion-controlled and that the lower value for Br_3^- can be ascribed to electrostatic repulsion.[24] The same may be true with our results.

Most of our studies of the reaction of phenoxide ions (Table II) were carried out in 0.1 M KBr, in which $[Br_3^-]/[Br_2]$ is 2 (whereas in 1.0 M KBr the ratio is 16). Under these conditions we found no significant reaction between Br_3^- and the anions of nitrophenols.[20] We assume that this applies to other phenoxides bearing electron-withdrawing groups, also. Similarly, phenol and Br_3^- do not appear to react significantly.[25]

Tribromination of Phenol. From the pH-rate profiles in Figure 1 it is clear that the facile tribromination of phenol arises because the mono- and dibromophenols, reacting via their anions, are effectively more reactive than phenol at intermediate pHs. However, if the pH is kept close to zero, where phenol is more reactive, predominant monobromination can be achieved. Similarly, when the reaction is carried out in acetic acid, where the ionization of phenols is less easy, monobromination (5.5% ortho, 94.5% para) is observed.[27]

Tribromination must occur by some combination of the pathways set out in Scheme I. Near pH 0, where the free phenols are the reactive forms, the rate constants are such that the principal route must be phenol → 4-bromophenol → 2,4-dibromophenol → 2,4,6-tribromophenol. However, at pH 5–7, where the reaction of the anions is dominant (Figure 1), there must be a significant contribution from other pathways. Such is the case since bromine attack at the ortho and para positions of phenoxide ion is essentially statistical, and both 2-bromophenol and 2,6-dibromophenol are more reactive than their isomers at such pHs (Figure 1).

Table V. Reaction Constants for the Bromination of Benzene Derivatives in Aqueous Solution[a]

Ph-X	k_2, M^{-1} s^{-1}	σ_p^+	ρ^+
$-O^-$	~1.2 × 10^9	-2[b]	~0
$-NMe_2$	3.6 × 10^8	-1.7	-2.2[c]
-OH	4.3 × 10^5	-0.920	−5.2
-OMe	3.7 × 10^4 [d,e]	-0.778	-7.0[d]
-Me	6.4 × 10^{-2}	-0.311	-10.7[f]
-H	1.1 × 10^{-5} [g]	0	-11.6,[f] -12.2[h]

[a] At 25 °C. Values of σ_p^+ are from ref 29, p 204. Apart from those for phenols and phenoxides, the values of k_2 and ρ^+ are from Dubois et al.[26,31-33] as indicated. [b] Reference 34. [c] Reference 32. The value of ρ^+ must be used with caution since it is based on rate constants close to the diffusion limit.[8] [d] Reference 26. [e] Cf. Tee, O. S.; Bennett, J. M. *Can. J. Chem.* **1984**, *62*, 1585. [f] References 31 and 33. [g] Statistically corrected. A value of (8.3 × 10^{-5} M^{-1} s^{-1})/6 was obtained earlier by extrapolation from higher temperatures: Berliner, E.; Gaskin, F. *J. Org. Chem.* **1967**, *32*, 1660. [h] Based on k_2 values for PhH, PhMe, and PhOMe. See eq 4 and Figure 4.

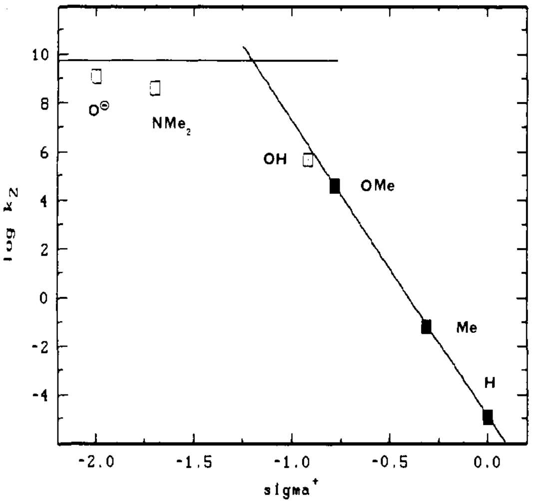


Figure 4. Hammett plot for the aqueous bromination of monosubstituted benzenes (data from Table V). The horizontal line corresponds to 5 × 10^9 M^{-1} s^{-1}, a "diffusion-controlled limit".[8] The correlation line through the points for PhH, PhMe, and PhOMe is given in eq 4.

Substituent Effects. As expected for a reaction involving a weak electrophile such as bromine,[2,28] the rate of bromination of phenols is markedly reduced by electron-withdrawing substituents (Table II). Such behavior may be treated by the Hammett equation,[28,29] and for seven para-substituted phenols[30] there is a reasonable correlation (r = 0.980) of log k_2 with σ_m^+ for which $\rho^+ = -5.21$.[12a]

For ortho-substituted phenols there is parallel behavior (Table II), although the salicylate (*o*-hydroxybenzoate) ion is anomalous.[12b] Compared to phenols, such ions show enhanced reactivities toward bromine and a lower selectivity ($\rho^+ = -2.7$) which we have ascribed to assistance from intramolecular proton transfer during the bromine attack.[12b] The bromination of 4-hydroxybenzoate ions is also anomalous (a *positive* value of ρ^+!) but for a different reason; such ions react via their 4-carboxyphenoxide tautomers.[12a]

The ρ^+ value of −5.2 for phenols may be compared to those for the aqueous bromination of other substituted benzenes. As seen in Table V, ρ^+ approaches zero as the electron-releasing ability of the primary substituent increases; that is, the aromatic substrates become less sensitive to substituent change as their reactivity toward bromine increases (see k_2, Table V). Likewise, ρ^+ for benzenes becomes less negative when the reactivity of the electrophile is increased.[28] These observations are in accord with the

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[24] Hojatti, M.; Kresge, A. J.; Wang, W.-H. *J. Am. Chem. Soc.* **1987**, 4023.

[25] Reaction between Br_3^- and some methoxybenzenes has been reported.[26] However, since the ionic strength was not kept constant as $[Br^-]$ was varied, the interpretation of the results is clouded.

[26] Aaron, J.-J.; Dubois, J.-E. *Bull. Soc. Chim. Fr.* **1971**, 603.

[27] de la Mare, P. B. D.; el Dusouqui, O. M. H.; Tillett, J. G.; Zeltner, M. *J. Chem. Soc.* **1964**, 5306. In acetic acid the bromination of phenol is very much slower: k_2 = 6.0 M^{-1} s^{-1}.

[28] Stock, L. M. *Aromatic Substitution Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1968.

[29] Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963.

[30] For the substituents: Me, *t*-Bu, H (18% ortho attack), COOH, COOEt, Br, and CN. The group COO^- was not included because the *p*-hydroxybenzoate ion reacts as its *p*-carboxyphenoxide ion tautomer.[12a]

reactivity-selectivity principle,[35] which operates widely, despite its failings.[36]

The rate constants for benzene, toluene, and methoxybenzene (Table V), which cover a range of 3 × 10^9, define an excellent straight line

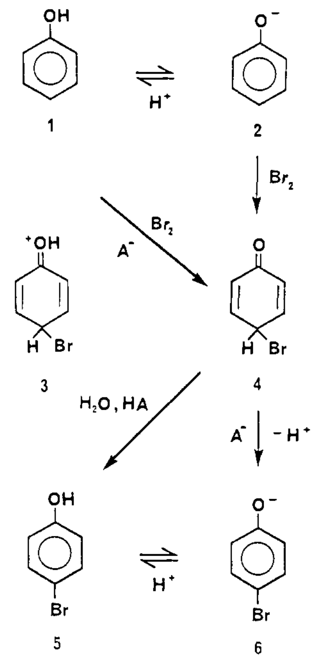
$$\log k_2 = -(4.97 \pm 0.02) - (12.2 \pm 0.05)\sigma_p^+;\ r = 0.999 \qquad (4)$$

As seen in Figure 4, the value for phenol is below this line,[37] but those for *N,N*-dimethylaniline and phenoxide ion are even further below. Such curvature in a linear free energy relationship may be due to the approach of the rate constants to the diffusion limit (Eigen curvature)[8,38,39] or to thermodynamic effects (Marcus curvature).[35,39] In the present case there is probably a combination of these effects since ρ^+ becomes less negative with increasing reactivity of the substrate (Table V) (Marcus curvature), but the reaction of the phenoxide ions is clearly diffusion-controlled, as discussed below.

The values of ρ^+ for the bromination of benzenes in water (−12.2 (eq 4)), trifluoroacetic acid (−12.3),[40] and acetic acid (−12.1)[28] are essentially the same even though the reactivities of the substrates vary enormously in these solvents.[27,40] Thus, it appears that solvent stabilization of the incipient Wheland intermediate is not of great significance. Rather, a change to a more polar solvent facilitates the departure of the developing bromide ion.

Diffusion-Controlled Rates. The normal model of solute diffusion, which is based on the Smoluchowski and Stokes–Einstein equations, predicts a rate constant of about 5 × 10^9 M^{-1} s^{-1} for the encounter of solute molecules of similar size (in water at 25 °C).[8,41] Many species react with bromine (and other halogens) with rate constants very close to this value, e.g., various enols and enolates,[8,42,43] enamines,[10,44] uracil anions,[14,45] the anion of malononitrile,[24] and at least one aniline.[32,46] Most of the phenoxide ions reported in this work behave likewise.

Scheme II



The 11 monosubstituted phenoxide ions in Table II, which includes the dianion of 4-hydroxybenzoic acid, react with bromine with values of k_2' in the range (1–9) × 10^9 M^{-1} s^{-1}, as do the 2,4- and 2,6-dibromophenoxide ions (Table I). The anions of 2- and 4-pyridone, which should have reactivities toward electrophiles like 2- and 4-cyanophenoxide ions,[47] react with k_2' values in the same range (Table III), as does the anion of 3-hydroxypyridine;[48] a total of 16 phenoxide ions, in all. Thus, unlike the situation referred to by Ridd in 1978,[49] there now seems little doubt that these phenoxide ions react with bromine at (or close to) the diffusion-controlled limit.

On the other hand, the anions of 2- and 4-pyrimidone (Table III) and of 2,4- and 2,6-dinitrophenol[6] react with bromine more slowly, as do pyridones, bromopyridones, and pyrimidones (Table III).[50] The anions of 3- and 5-bromo-2-pyridone (Table III) are borderline cases. Thus, it appears necessary to have one or more electron-withdrawing substituents of combined $\sigma^+ > 0.9$ to reduce the value of k_2' appreciably below the diffusion-controlled limit.[51]

Mechanism. The principal features of the (dominant) para bromination of phenol are as set out in Scheme II. Bromine attack on phenol **1** (pH < 4.5) or its anion **2** (pH > 4.5) leads to the observable[5a,b] cyclohexadienone **4**. The former attack is probably general base-catalyzed,[5c,12b,53] in which case the protonated dienone **3** may be avoided.

Enolization of the dienone **4** is catalyzed by general acids and by general bases.[5a,b,d] The former shows a very low Brønsted α value, and the unstable protonated dienone **3** appears not to be

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(31) Dubois, J.-E.; Aaron, J.-J.; Alcais, P.; Doucet, J. P.; Rothenberg, F.; Uzan, R. *J. Am. Chem. Soc.* **1972**, *94*, 6823. Note: the rate constants in Table I of this paper are for specific positions, and they have not been corrected for the formation of Br_3^-. As a result, they are lower than otherwise.[26,32,33]

(32) Uzan, R.; Dubois, J.-E. *Bull. Soc. Chim. Fr.* **1971**, 598.

(33) Rothenberg, F.; Alcais, P.; Dubois, J.-E. *Bull. Soc. Chim.* Fr. **1971**, 598.

(34) There are various literature estimates of σ_p^+ for the oxido substituent (—O⁻) in the range -1.62 to -2.3, with most being close to -2. See: de la Mare, P. B. D.; Newman, P. A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1797.

(35) Pross, A. *Adv. Phys. Org. Chem.* **1977**, *14*, 69.

(36) Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755.

(37) If phenol is included in the least-squares analysis, the correlation line is decidedly worse ($r = 0.998$) and $\rho^+ = -11.7 \pm 0.4$.

(38) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(39) Bell, R. P. In *Correlation Analysis in Chemistry: Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 2. Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: Oxford, England, 1985; Chapter 10 and references therein.

(40) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 7599.

(41) (a) Laidler, K. J. *Chemical Kinetics*, 3rd ed.; Harper and Row: New York, 1987; p 212ff. (b) Moelwyn-Hughes, E. A. *The Chemical Statics and Kinetics of Solutions*; Academic Press: London, England, 1971; Chapter 5. (c) Benson, S. W. *The Foundation of Chemical Kinetics*; McGraw-Hill: New York, 1960; pp 494–502. (d) Hammes, G. G. *Principles of Chemical Kinetics*; Academic Press: New York, 1978; pp 62–67. (e) Entelis, S. G.; Tiger, R. P. *Reaction Kinetics in the Liquid Phase*; Wiley: New York, 1976; Chapter 1. (f) Jordan, P. C. *Chemical Kinetics and Transport*; Plenum Press: New York, 1979; Chapter 9. (g) For more advanced and abstruse treatments, see: Rice, S. A. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Compton, R. G., Eds.; Elsevier: Amsterdam, 1985; Vol. 25.

(42) The older literature, reviewed by Ridd,[8] has several rate constants above 10^{10} M^{-1} s^{-1} for the attack of halogens on enols and enolates. They were based on estimates of enol contents which are now considered unreliable: Toullec, J. *Adv. Phys. Org. Chem.* **1981**, *18*, 1.

(43) Dubois, J.-E.; Toullec, J. *Tetrahedron* **1973**, *29*, 2859. Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393. Tapuhi, E.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 5758. Guthrie, J. P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* **1984**, *106*, 1351. Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392. Keefe, J. R.; Kresge, A. J.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224. Hochstrasser, R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1988**, *110*, 7875.

(44) Tee, O. S.; Thackray, D. C.; Berks, C. G. *Can. J. Chem.* **1978**, *56*, 2970.

(45) The anion of 6-azauracil is less reactive, $k_2 \sim 10^6$ M^{-1} s^{-1}: Banerjee, S.; Tee, O. S. *J. Org. Chem.* **1976**, *41*, 4004.

(46) Many anilines react with nitrosyl halides at diffusion-controlled rates.[8]

(47) The value of σ_m^+ for aza nitrogen is 0.54,[16] close to that (0.56) for cyano.[29]

(48) For the anion of 3-hydroxypyridine $k_2' = 1.4 \times 10^9$ M^{-1} s^{-1}: Tee, O. S.; Bennett, J. M., unpublished results.

(49) Ridd wrote of Bell's work:[6] "Unfortunately there are too few substituents to provide clear evidence for a limiting reaction rate."[8]

(50) For $=NH^+—$ as a substituent in a benzene ring σ_m^+ is close to 2.[16]

(51) Unfortunately, it is not possible to have a simple set of substituted phenoxide ions which span the range of reactivity 10^8–10^{10} M^{-1} s^{-1}, with which one might analyze the curvature in the transition region.[52] Polysubstituted derivatives are to be avoided because their substituent effects are not simply additive.[31]

(52) The reactivities of five acetophenone enols toward bromine, $k_2 = (2.0\text{–}4.3) \times 10^9$ M^{-1} s^{-1}), appear to vary systematically with the substituent on the aryl ring. See: Hochstrasser, et al., in ref 43.

(53) Bromine attack on phenol, 4-methylphenol, and 4-bromophenol exhibits buffer catalysis: (a) Iyengar, N. R. Ph.D. Thesis, Concordia University, Montréal, 1985. (b) Tee, O. S.; Iyengar, N. R., manuscript in preparation.

involved.[5b,d] Thus, it seems that **3**, which is a Wheland intermediate[2] (benzenonium ion)[28] stabilized by hydroxyl, is not involved in either the formation *or* the decomposition of the dienone **4**.

Phenols with electron-withdrawing substituents are less reactive toward bromine (k_2, Tables I and II), and reaction of their anions becomes more and more important (Figures 1 and 2). The resulting dienones must enolize faster[5b] than **4** and so be only transitory. This explains why the para-substituted phenols studied by Kulic and Vecera[9] had the same rate constant for substrate decrease and product increase,[54] giving rise to the erroneous belief that dienones such as **4** are not observable in aqueous solution.

Recent, elegant studies by Kochi and co-workers implicate charge-transfer complexes and radical-ion pairs in electrophilic aromatic substitution in nonaqueous media.[40,55] Such species, if involved in the aqueous bromination of phenol, must collapse very rapidly to the observable cyclohexadienone, **4**.[56]

Experimental Section

All of the phenols, except one, were obtained from commercial sources. Any samples which were old or discolored were purified by distillation or recrystallization. 2,6-Dibromophenol was prepared by the decarboxylation of 3,5-dibromo-4-hydroxybenzoic acid.[57] All buffer components and inorganic reagents were of the highest purity available.

For the most part, procedures for making up solutions and measuring kinetics followed past practice.[5,10-12] *Fresh* stock bromine solutions (0.1 M in 0.1 or 1.0 M aqueous KBr) were made up by weight,[58] and then a small volume was diluted with the desired medium. Due to the poor solubility of most of the phenols in water, stock substrate solutions (0.05–0.50 M) were prepared in HPLC grade methanol. Small volumes of these were diluted with the desired medium.

The concentrations of substrate and bromine were normally 0.50 and 0.05 mM, respectively, after 1:1 mixing in the stopped-flow apparatus. In a few cases, these concentrations were reduced to slow down the faster reactions. The actual concentrations used are given in the tables in the Supplementary Material.

Solutions had a total ionic strength of 0.11 or 1.0 M (= KBr + other electrolyte + ionized buffer), as indicated in the tables, except at the lowest pHs where it rises above these values due to the concentration of acid used. Buffer solutions were prepared as previously.[5,10-12]

Rates were measured at 25.0 ± 0.1 °C by monitoring the disappearance of bromine around 265 nm (tribromide ion band)[14] by using an Aminco-Morrow stopped-flow apparatus + Aminco DW-2 spectrophotomoter connected to a Biomation 805 waveform recorder.[44] In the earlier work (Tables I, III, and IV)[1a] the stored curve was plotted out onto large graph paper, digitized, and then analyzed.[44] For the later studies,[1b] the waveform recorder was interfaced to an Apple II microcomputer.[59] In cases where the decay of transient cyclohexadienones[5] interfered with the infinity readings, the monitoring wavelength was set at 275 nm.

For a 10- (or more)-fold excess of substrate over bromine the absorbance decays exhibited good first-order behavior. Pseudo-first-order rate constants, evaluated from data covering about 90% reaction, were converted to second-order constants (k_2^{obsd}) by correction for the substrate concentration[14] and for the fraction of free bromine in equilibrium with Br_3^- and at the higher pHs, HOBr, and its anion.[11b,14] The dissociation constant of Br_3^- was taken as 0.0625 M (I = 1.0 M) and 0.0562 M (I = 0.1 M).[13] In some cases, where the excess of substrate was not very large, the absorbance traces were directly analyzed for second-order behavior.[10b] This provided a check of the rate law and also allowed some very fast rates to be measured. It should be noted that the measurement of the largest rate constants (up to 5×10^8 M^{-1} s^{-1}, Table S1) was only possible because of the very low concentration of free bromine at high pH.[11b,14] Generally speaking, the reproducibility of the rate constants was 5% (or better) for the slower reactions and about 10% for the faster ones.

For analysis of the products of phenol bromination a Perkin-Elmer F11 gas chromatograph was used with a 3 ft stainless steel column packed with Chromosorb-W HP which was coated with Carbowax 20M. The column was maintained at 145 °C and the conductivity detector at 100 °C. A calibration graph of peak height ratio vs weight ratio was constructed with the trimethylsilyl ethers prepared from accurately weighed mixtures of 2- and 4-bromophenols. Retention times were in the following order: phenol < 2-bromophenol < 4-bromophenol. By using the above calibration, the proportions of the two bromophenols were determined for brominations carried out at pH 1, 7, and 10–11.

Bromine (200 mL of 12.5 mM in 1 M aqueous KBr) and phenol (200 mL of 125 mM in 1 M KBr) were mixed in one motion in 300 mL of 1 M KBr, with rapid stirring, and the mixture was allowed to stand for 1 h. The resulting solution was acidified with concentrated HCl, filtered to remove any precipitate of 2,4,6-tribromophenol, and extracted with 2 × 200 mL portions of chloroform. After reducing the volume of the extracts to 10 mL, 5 mL of hexamethyldisilazane was added, the mixture was filtered, and the filter paper was washed with chloroform. The volume of the filtrate was reduced to 5 mL, further silylating agent was added to bring the volume to 10 mL, and the mixture was left for 24 h.

For qualitative and quantitative comparisons the TMS ethers of phenol, the bromophenols, and known mixtures of them were likewise prepared from chloroform solution, using a large excess of HMDS. Unfortunately, the TMS derivatives from the di- and tribromophenols did not elute from the GC column used.

The pK_a of 2,4,6-tribromophenol was determined to be 5.93 (at 25 °C, I = 0.1 M (KBr)) by using UV-vis spectrophotometry.[60]

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Appendix

Consider the reaction scheme:

$$A + B \xrightarrow[\text{slow}]{k_2} C \xrightarrow[\text{fast}]{B} \text{products} \qquad (A1)$$

With $[A]_0 = a$, $[B]_0 = b$, and $(b - x)$ as the amount of B remaining at time t, the rate of disappearance of B is

$$\text{rate} = \frac{-\mathrm{d}(b-x)}{\mathrm{d}t} = \frac{\mathrm{d}x}{\mathrm{d}t} = 2k_2\left(a - \frac{x}{2}\right)(b - x) \qquad (A2)$$

For the specific condition $b = 2a$ the differential equation simplifies to $\mathrm{d}x/\mathrm{d}t = k_2(b - x)^2$, integration of which leads to[61] $1/(b - x) = 1/b + k_2 t$. Thus, monitoring the disappearance of B and analyzing the data in terms of this expression should yield an estimate of the *true* rate constant (k_2) for the first step of the scheme shown in eq A1. This situation arises because the doubling of the rate (eq A2) is counterbalanced by having $2[A]_0 = [B]_0$.

Likewise, if A reacts with one molecule of B in the rate-limiting step but consumes three molecules overall, the *true* value of k_2 is accessible by imposing the initial condition $3[A]_0 = [B]_0$. As developed in detail elsewhere by Paventi,[1a,62] this approach[63] is even more general in that it is not mandatory that the first step of the sequence be rate-limiting. Provided the initial concentrations match the overall stoichiometry of the reaction, data analysis should provide the second-order rate constant of the rate-limiting step, wherever it occurs in the reaction sequence.[1a,62]

The above conclusions are the basis for the experiments reported in Table IV for probing the dibromination of 4-bromophenol and the tribromination of phenol.

Note Added In Proof. The traditional Smoluchowski/Stokes–Einstein approach to diffusion-controlled rate constants has recently been scrutinized: Olea, A. F.; Thomas, J. K. *J. Am. Chem.*

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(54) In the case of 4-methylphenol they apparently did not notice the ~10% of bromine attack that occurs ipso to the methyl.[5a,c]

(55) Sankararaman, S.; Haney, W. A.; Kochi, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7824; **1987**, *109*, 5235. Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 7240 and references therein.

(56) We have been unsuccessful in detecting the 2-bromo-3,5-cyclohexadienone which is presumably involved in ortho bromination.[5a,b]

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(58) Tee, O. S.; Bennett, J. M. *Can. J. Chem.* **1984**, *62*, 1585.

(59) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.

(60) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 3rd ed.; Chapman and Hall: London, England, 1984; Chapter 4.

(61) See: Laidler,[40a] p 23ff.

(62) Paventi, M. *Can. J. Chem.* **1987**, *65*, 1987.

(63) This approach is alluded to in the latest edition of Laidler's book,[40a] p 27.

Soc. **1988**, *110*, 4494. For the systems studied, the Smoluchowski equation worked well with *measured* diffusion constants but not with those estimated by the Stokes-Einstein equation.

Registry No. Bromine, 7726-95-6; tribromide ion, 14522-80-6; 2,4,6-tribromophenol, 118-79-6; 2,4,6-tribromophenol anion, 65800-38-6; phenol, 108-95-2; phenoxide, 3229-70-7; 2,4-dimethylphenol, 105-67-9; 2,6-dimethylphenol, 576-26-1; 2-nitrophenol, 88-75-5; 2-nitrophenoxide, 16554-53-3; 3-nitrophenol, 554-84-7; 3-nitrophenoxide, 16554-54-4; 4-cyanophenol, 767-00-0; 4-cyanophenoxide, 14609-76-8; 4-nitrophenol, 100-02-7; 4-nitrophenoxide, 14609-74-6; 2-pyrimidone, 557-01-7; 2-pyrimidone anion, 33631-11-7; 4-pyrimidone, 4562-27-0; 4-pyrimidone anion, 3273-54-9; 4-bromophenol, 106-41-2.

Supplementary Material Available: Tables of second-order rate constants for the bromination of phenols and pyrimidones as a function of various concentrations (Tables S1-S5) (5 pages). Ordering information is given on any current masthead page.

Matrix-Isolation Decay Kinetics of Triplet Cyclobutanediyls. Observation of Both Arrhenius Behavior and Heavy-Atom Tunneling in C-C Bond-Forming Reactions

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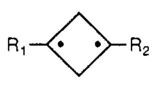
Abstract: The ring-closure reactions of a variety of triplet 1,3-cyclobutanediyls (**1**) have been observed by EPR spectroscopy under matrix-isolation conditions. It is shown that matrix-site effects can be very well modeled by a Gaussian distribution of activation energies with a standard deviation of ca. 0.5 kcal/mol. Several new techniques have been developed to model such dispersive kinetics. Structures **1** with delocalizing substituents (vinyl, phenyl) show conventional Arrhenius behavior, with log A = 6-8 and E_a = 1-2 kcal/mol. Fully localized cyclobutanediyls ring close via quantum mechanical tunneling. A model emphasizing the differing well depths of the singlet biradicals is developed to rationalize these contrasting behaviors.

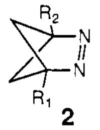
The direct spectroscopic characterization of reactive intermediates has been a major focus of modern mechanistic chemistry. Through such studies, one can determine whether the thermodynamic and kinetic properties of a reactive intermediate are consistent with those ascribed inferentially on the basis of product distributions, stereochemical labeling, and other classical techniques. Laser-flash photolysis and related fast spectroscopy techniques have often been successfully applied to such studies. However, there are many types of reactive intermediates that do not have a well-characterized chromophore and an unambiguous, efficient mode of generation. Both of these are necessary for the laser-flash methods, which generally have relatively low spectroscopic resolution. The matrix-isolation technique is an alternative approach for providing high-resolution spectroscopic data on reactive structures. However, for kinetic studies, it has been less broadly successful, at least in part because of "matrix-site effects". In a nonfluid medium at cryogenic temperatures, different molecules in a sample experience different microenvironments. These matrix perturbations generally lead to complex (dispersive) kinetic behavior, because, in principle, each site has its own intrinsic decay rate.

We have recently reported the synthesis and EPR spectroscopy of several 1,3-disubstituted 1,3-cyclobutanediyls (**1**), the first series of directly observed, localized 1,3-biradicals.[2] We now describe the matrix-isolation decay behavior of several members of the series as monitored by EPR spectroscopy. For the purpose of discussion, it is convenient to divide the cyclobutanediyls into two classes, those with delocalizing substituents and those without. We shall refer to the first group (**1**-Vin, **1**-EV, **1**-Ph) as stabilized and the second (**1**-Me, **1**-Et) as fully localized.

We have made a considerable effort to address the matrix-site problem and have developed several new techniques and analytical approaches. This report contains much description of methodology and of detailed efforts to accurately quantify the results obtained. In the course of such discussions, one can lose sight of the more far-reaching, general findings of the work. We therefore summarize, at the outset, the important qualitative conclusions we have reached concerning the decay of triplet cyclobutanediyls.



1



2

1-H	$R_1 = R_2 = H$
1-Me	$R_1 = R_2 = CH_3$
1-Et	$R_1 = R_2 = CH_2CH_3$
1-Vin	$R_1 = R_2 = CH{=}CH_2$
1-Ph	$R_1 = R_2 = Ph$
1-EV	$R_1 = CH_2CH_3$ $R_2 = CH{=}CH_2$

First, by using a novel technique termed "distribution slicing", we have been able to demonstrate unambiguously for **1**-Vin, **1**-EV, and **1**-Ph that there *is* a matrix-site effect. That is, photolysis of diazabicyclohexenes (**2**) in frozen-solvent matrices produces cyclobutanediyls (**1**) in a range of matrix sites with differing decay behaviors. Importantly, the distribution-slicing method clearly shows that there is a distribution of E_a values among the matrix sites. This rules out one type of analysis which assumes a distribution of Arrhenius preexponential terms (A), with a constant E_a. More detailed analysis strongly indicates that the rate distribution is primarily a consequence of a distribution over E_a and is relatively insensitive to any variation in A. In addition, the distribution-slicing method provides qualitative information on the width and the shape of the rate distribution. We find that a Gaussian distribution of E_a values is an excellent model for these systems.

Second, by combining distribution slicing with a new method of directly fitting decay traces, we have been able to obtain most probable decay rates over a sizable temperature range for **1**-Vin, **1**-EV, and **1**-Ph. These rates clearly follow the Arrhenius law. These structures are the first localized 1,3-biradicals for which

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[1] (a) NSF Predoctoral Fellow, 1982-1985. (b) JPL-CSMT Fellow, 1987-1988.

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