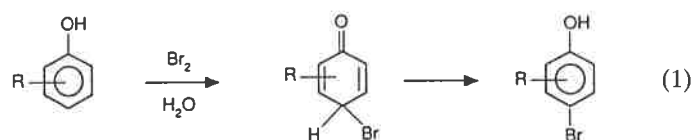


Phenols react readily with bromine to undergo electrophilic substitution at ortho and para positions. In broad outline, the reaction involves bromine attack, resulting in the formation of a bromocyclohexadienone, followed by enolization of the intermediate to the bromophenol product :

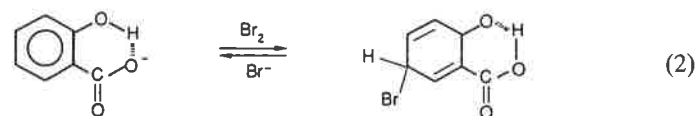


During the last few years we have studied both steps of this bromination, in aqueous solution. What appears to be a simple, classic example of aromatic electrophilic substitution is not so simple, and not so classical.

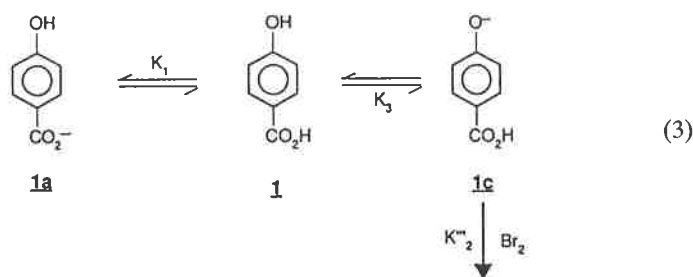
Simple phenols react with molecular bromine via the phenol at low pH and the phenoxide ion at higher pH [1]. The changeover between these two modes of reaction depends on the reactivity of the phenol and its pK_a , such that less reactive phenols (eg. nitrophenols) react as their anions even at pHs close to zero. The attack of bromine on simple phenoxide ions is essentially diffusion controlled [1-3] and so the reactivity of phenols reacting as their anions is determined primarily by their acidity [1].

The well-known, facile tribromination of phenol arises because mono- and dibromophenols, reacting via their anions, are effectively more reactive than phenol at intermediate pHs. However, if the pH is kept near zero, where phenol is more reactive, predominant monobromination (82 % para) occurs [1].

As expected for a relatively weak electrophile, bromine attack on simple phenols is quite sensitive to the substituent, with a Hammett $\rho^+ = -5.2$ [1-2]. However, salicylate anions (2-hydroxybenzoate ions) seem anomalous ; they show enhanced reactivity and much lower selectivity : $\rho^+ = -2.7$ [3]. This behaviour we have ascribed to intramolecular proton transfer assisting bromine attack :



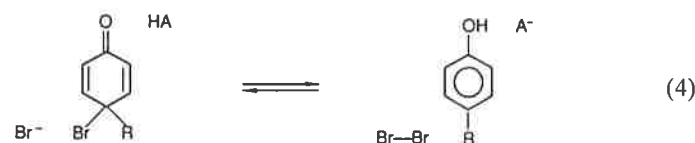
The rates of brominations of 4-hydroxybenzoate ions (initially envisaged as "controls" for the salicylate study) were also found to be anomalous : the 3-bromo-4-hydroxybenzoate ion appears to be more reactive than the 4-hydroxybenzoate ion and 5200 times more reactive than expected. Thus, the reaction has an apparent ρ^+ which is positive ! This anomaly is removed, however, if the 4-hydroxybenzoate ions react as their 4-carboxyphenoxide tautomers [2] :



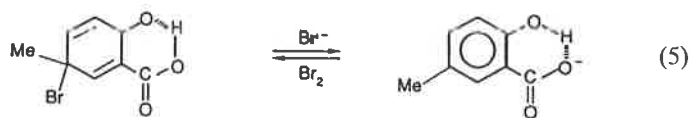
During routine kinetic measurements of the rate of phenol bromination we noted a slight drift in the UV absorbance traces. This led us to discover the transient 4-bromo-2,5-cyclohexadienone [4], which is the key intermediate in the dominant, para bromination of phenol. Other transient dienones, derived from alkylphenols and naphthols, were subsequently observed and studied [4-8].

Enolization of these dienones is catalyzed by general acids and general bases, and it exhibits significant isotope effects [4-6]. Deprotonation by general bases leads simply to the anion of the bromoproduct, but the general acid catalysis is unusual ; it appears to have a small, negative Bronsted α which was tentatively attributed to a termolecular mechanism [5-6].

In the case of p-alkylphenols about 10 % of the bromine attack occurs ipso to the alkyl group, leading to the formation of "ipso-dienones" [4-7]. These labile species decompose by debromination, which is bromide ion induced and general acid-catalyzed [7]. This result implies that the microscopic reverse reaction, bromine attack on the parent phenol, takes place with general base catalysis (4) [7]. Such behaviour was observed in separate experiments for phenol, 4-methylphenol, and 4-bromophenol, where the reaction of these substrates with bromine was found to be catalyzed by buffer bases [9].



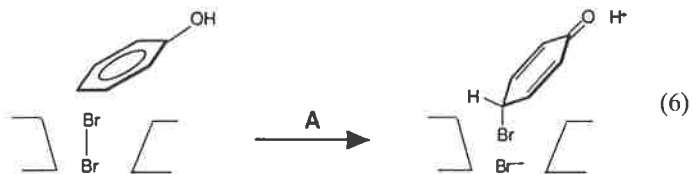
In support of the foregoing, debromination of the ipso-dienone derived from 5-methylsalicylic acid is catalyzed by its carboxyl group (5), but not by external acids [3-7]. Also, as outlined above, bromine attack on salicylate ions is believed to be assisted by intramolecular proton transfer (2).



The mechanism shown in (5) can also operate with a metal ion (eg. Cu^{2+} , Fe^{3+}) in place of the carboxyl proton, since salicylate dianions forms strong complexes with such ions. Metal ion catalysis was also found for a related dienone enolization [8].

Cyclodextrins (CDs) are "bucket-shaped" cyclic oligomers of glucose which form host-guest complexes in aqueous solution with many inorganic and organic species [10], including molecular bromine and phenols. Hence, we hoped that these "promiscuous" molecular hosts [11] would induce novel "supramolecular" effects [12] on the aqueous bromination of phenols. We were not disappointed.

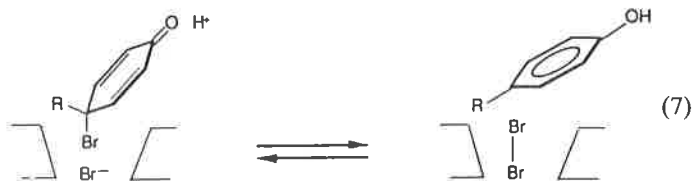
Initial experiments with α -cyclodextrin (α -CD) [10] showed complex kinetic behaviour, which was due expected equilibria, and to an additional equilibrium involving the complexation of tribromide ion [13]. We then showed that the reaction of bromine with phenols and phenoxide anions is modestly catalyzed by α -CD [14]. The effects of substituents differ little from those in the normal reaction in aqueous solution and so the CD catalyzed process was interpreted in terms of reaction between the free phenol and the CD. Br_2 "supermolecule", rather than the alternative of free Br_2 reacting with the CD. phenol inclusion complex [14-15] (6).



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The effects of α CD on the enolization of transient cyclohexadienones were found to be small, complex and not easily analyzed. In contrast, the debromination of ipso-dienones exhibited substantial (tractable) catalysis for several p-alkyl groups. Substituent effects are minimal, and consistent with reaction between the ipso-dienone and the weak CD. Br^- complex [15-16] :



Thus, two distinct studies [14-16] led us the same description of the common transition state for bromination and debromination : the bromine atoms are more or less inside the CD cavity, the organic moiety outside [14-16].

We also examined the debromination of the ipso-dienone in (5) in the presence of α -CD. This system was studied to see how two very different types of catalysis interact : constructively, passively, or destructively. We found that the reaction is strongly catalyzed by α -CD, and to the same extent as other ipso-dienones [16]. The combination of intramolecular general acid catalysis by the 2-carboxyl group and catalysis by α -CD leads to an overall rate enhancement of 12 000 000 !

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