The Bromination of Salicylate Anions. Evidence for the Participation of the Ortho Carboxylate Group

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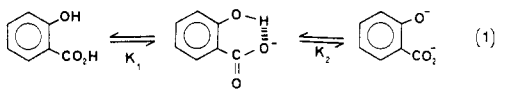
Salicylate monoanions show reduced selectivity toward bromine in aqueous solution when compared to similarly substituted phenols. In particular, 5-substituted salicylate ions show $\rho^+ = -2.69$ whereas for para-substituted phenols $\rho^+ = -5.21$. From this and other evidence it is argued that bromine attack on such ions may involve proton transfer from the hydroxyl group to the *o*-carboxylate to which it is hydrogen bonded. 5-Methylsalicylic acid (**8a**) forms, in part, an unstable cyclohexadienone (**13**) resulting from ipso bromine attack. The breakdown of **13** shows intramolecular catalysis by the *o*-COOH group, which has an effective molarity of 58 M. The microscopic reverse reaction of bromine on the anion of **8a** must, therefore, involve the *o*-CO_2^- group, as suggested above. Implications with respect to the activating effect of hydroxyl groups on cation-forming reactions are discussed.

Recent studies in this laboratory have been concerned with the mechanism of bromination of phenols in aqueous solution.[1-3] Of particular note, we found that one can observe transient 4-bromo-2,5-cyclohexadienones during the reaction of bromine with phenol and with methylated phenols.[1a] As a result, we were able to study the enolization of such dienones to 4-bromophenols in some detail.[1b] The present paper describes a study of the bromination of salicylic acids (*o*-carboxyphenols), the object being to see if the *o*-carboxyl (or carboxylate) group altered the pattern of behavior shown by other phenols. For comparative purposes we initially studied the bromination of *p*-hydroxybenzoic acid (*p*-carboxyphenol) but found its reactivity to be sufficiently unusual to warrant a separate detailed study.[3]

Salicylic acid (1) possesses abnormal acid dissociation constants in aqueous solution. Its first ionization occurs relatively easily ($pK_1 = 2.98$), whereas its second ionization is quite difficult ($pK_2 = 13.61$).[4] By way of comparison,

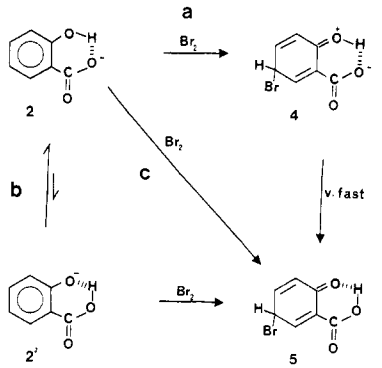


(1)

1 2 3

p-hydroxybenzoic acid has pK_a values that are more normal for a benzoic acid ($pK_1 = 4.61$) and for a phenol ($pK_2 = 9.31$).[5] It has also been found that the deprotonation of various salicylate ions (such as **2**) by hydroxide ion is relatively slow ($k_{OH} \sim 10^7$ M^{-1} s^{-1}) for a phenol[6] and that the protonation of **2** by hydronium ion is slow for a carboxylate ion.[7] These abnormalities are believed to be due to an intramolecular hydrogen bond between the hydroxyl group and the adjacent carboxylate function of the salicylate monoanion (see structure **2**, eq 1).[6,7] Support for this view comes from various studies on substituted salicylate anions,[6b] and Hibbert has recently shown that the anomalously slow deprotonation (eg. **2** → **3**) results from base attack at a normal rate on a small (~0.1%) equilibrium amount of the monoanion lacking the internal hydrogen bond,[6b] as suggested earlier by Eigen.[6a]

Scheme I. Three Possible Pathways for the Bromination of Salicylate Ion 2 Leading to the Dienone 5



The present study of the bromination of salicylic acid represents an attempt to determine if the internal hydrogen bond in **2** affects, in any way, the normal course of phenol bromination. Judging from the available literature,[1,2,8,9] the bromination of a phenol in water at low pH involves bromine attack to give a protonated cyclohexadienone[10] which undergoes rapid proton loss to give free cyclohexadienone.[1] The latter tautomerizes to the substitution product and in some cases this process is slow enough (relative to bromine attack) to be observed.[1] At higher pH bromine attack is on the phenoxide anion[2,8,9] which leads to the intermediate cyclohexadienone directly.

Our initial hypothesis for the bromination of the salicylate anion **2** may be appreciated by reference to Scheme I in which we depict three possible routes from **2** to the transient cyclohexadienone **5**. The first, labeled a, involves bromine attack on **2** to give the zwitterionic intermediate **4**, which rapidly transfers a proton internally to give **5**. The second pathway (b) has the sequence of events reversed: internal proton transfer converts **2** to its tautomer **2'** which is attacked by bromine to give **5**. The third and most interesting route (c) has bromine attack and proton transfer occurring more or less in concert so that **2** is converted directly to **5**.

(1) (a) Tee, O. S.; Iyengar, N. R.; Paventi, M. *J. Org. Chem.* **1983**, *48*, 759. (b) Tee, O. S.; Iyengar, N. R.. *J. Am. Chem. Soc.* **1985**, *107*, 455.
(2) Paventi, M. Ph.D. Thesis, Concordia University, Montreal, 1984. Tee, O. S.; Paventi, M., manuscript in preparation.
(3) Tee, O. S.; Iyengar, N. R.; Kraus, B. *J. Org. Chem.* **1985**, *50*, 973.
(4) Perrin, D. D. *Nature (London)* **1958**, *182*, 741.
(5) Kortum, G.; Vogel, W.; Andrussow, K. "Dissociation Constants of Organic Acids in Aqueous Solution"; Butterworths: London, 1961; *Pure Appl. Chem.* **1961**, *1*, 190.
(6) (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. (b) Hibbert, F. *Acc. Chem. Res.* **1984**, *17*, 115 and references cited therein.
(7) Bell, R. P. "The Proton in Chemistry"; Cornell University Press, Ithaca, NY, 1973; pp 130–131.
(8) Bell, R. P.; Rawlinson, D. J. *J. Chem. Soc.* **1961**, 63.
(9) Kulic, J.; Vecera, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 71.
(10) The involvement of the protonated cyclohexadienone is not mandatory. In aqueous solution it will be a high-energy species[1b] which may be avoided by general catalysis. Certainly, this seems to be the case for the enolization of the cyclohexadienones recently studied.[1b] The present work (and other studies in progress) suggest that it may be avoided during bromine attack also (see Discussion).

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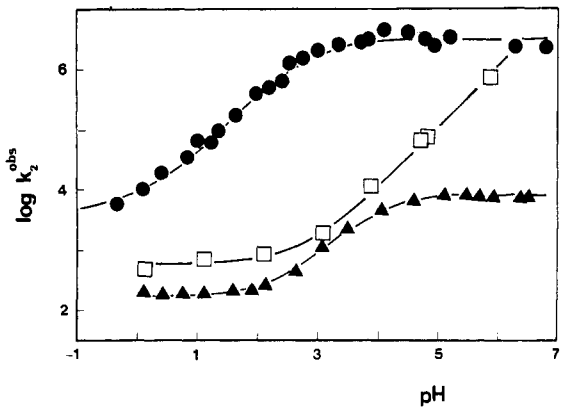


Figure 1. pH–rate profiles for the reaction of bromine with salicylic acid (1) (●), methyl salicylate (6) (□), and *o*-anisic acid (7) (▲).

Pathway a represents the (presumed) normal type of pathway followed by phenols. Substituent effects should be similar to those for ordinary phenols ($\rho \sim -5$)[3] but may be attenuated by the presence of the intramolecular bond in the zwitterion **4** which should exert a stabilizing effect. Pathway b, which involves bromine attack on the minor tautomeric anion **2′**, must be given serious consideration since phenoxide ions react with bromine at diffusion-controlled rates.[2,3,8,9] Furthermore, we have recently shown that *p*-hydroxybenzoate ions react via an analogous pathway.[3] As found in that work,[3] substituent effects for pathway b should be opposite to normal; electron-withdrawing groups should speed-up the reaction as they increase the proportion of the tautomer **2′** but barely affect the rate of bromine attack on **2′** (since $\rho \sim 0$).[2,3]

From the outset we were intrigued by the possibility of pathway c. The zwitterion **4** should have a very short lifetime; it has a very acidic proton ($pK < -3$)[11] hydrogen bonded to a carboxylate oxygen ($pK \sim 3$) (vide infra), and so the intramolecular proton transfer converting **4** to **5** should be exergonic ($\Delta G_0 > 8$ kcal/mol) and very fast.[6a] If this proton transfer is faster than Br^- can diffuse away from **4** the conversion of **2** to **5** will appear to be concerted even though bromine attack and proton transfer are asynchronous. Alternatively, the two processes may be synchronous and the conversion **2** to **5** be truly concerted. In either case (synchronous or asynchronous), pathway c should show attenuated substituent effects compared to normal phenol bromination.

One further possibility was considered: the *o*-carboxyl group in the intermediate cyclohexadienone[13] **5** might facilitate its tautomerization to product anion (5-bromosalicylate). However, we were unable to observe **5** and so to pursue this point. On the other hand, the dienone derived from ipso bromine attack[1a] on 5-methylsalicylic acid was observed and studied.

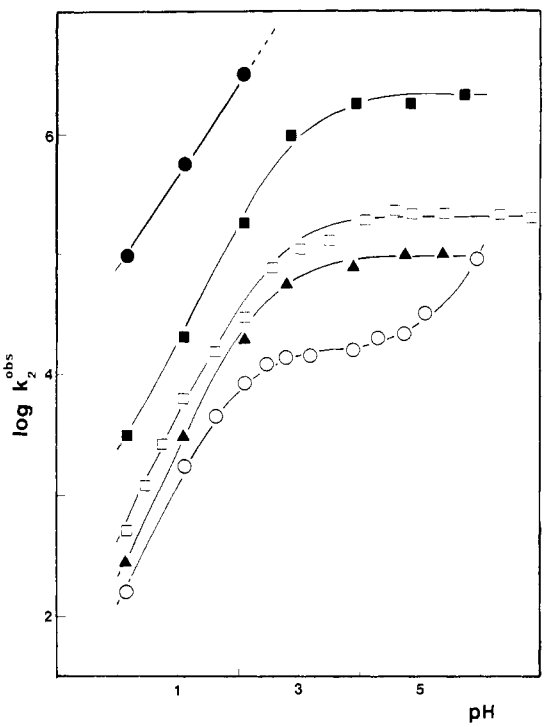
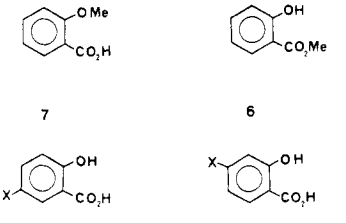


Figure 2. pH–rate profiles for the reaction of bromine with substituted salicylic acids: 4-methyl (●), 5-methyl (■), 5-bromo (□), 5-sulfo (▲), 5-nitro (○). The profiles for 4-chloro and 5-formyl are very close to those of 5-methyl and 5-nitro, respectively, and so they have been omitted for the sake of clarity.

Results

We have measured the kinetics of bromination of salicylic acid (**1**), methyl salicylate (**6**), *o*-anisic acid (**7**), and several substituted salicylic acids (**8**, **9**). The media used



7 6

8 9

a, X = Me
b, X = CHO
c, X = Br
d, X = SO_3^-
e, X = NO_2

a, X = Me
b, X = Cl

were 0.1 M aqueous KBr solutions buffered in the pH range 0–7. Under these conditions the formation of hypobromous acid is either negligible or can be corrected for easily.[2,19] Most of the substrates react rapidly with bromine, necessitating the use of the stopped-flow method.[3,19,20] In all cases second-order behavior was observed at fixed pH: first-order in both substrate and bromine. The reported values of the observed second-order rate

(11) Judging by the protonation p*K*s of cyclohexadienones which cannot enolize[12] the pK_a of the OH proton of **4** must be less than −3.
(12) (a) Vitullo, V. P.; Grossman, N. *J. Am. Chem. Soc.* **1972**, *94*, 3844. (b) Cook, K. L.; Waring, A. J. *J. Chem. Soc., Perkin Trans. 2* **1973**, 84.
(13) Before we recently showed that cyclohexadienones are observable for some phenols[1] the existing literature for aqueous bromination suggested otherwise. Kulic and Vecera[9] reported that bromine decrease and product increase occur at the same rate for para-substituted phenols. Zollinger,[14] citing a personal communication from Shilov, states that there is no primary hydrogen isotope effect in the bromination of phenol-2,4,6-d_3 in aqueous HBr. There is a reference to the same effect in the Russian literature.[15] Similarly, Grovenstein et al.[16] reported no isotope effect in bromination of 2,4-dibromophenol in aqueous HBr, although isotope effects are observable in the iodination of phenols.[16] However, cyclohexadienones have been observed in the bromination of 2,6-dialkylphenols in acetic acid.[17,18]
(14) Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 163.
(15) Vainstein, F. M.; Shilov, E. A.; Grishin, O. M. *Zh. Vses. Khim. Ova. im. D. I. Mendeleeva* **1960**, *5*, 119; *Chem. Abstr.* **1960**, *54*, 24492e.
(16) Grovenstein. E., Jr.; Aprahamian, N. S.; Bryan, C. J.; Gnanapragasam, N. S.; Kilby, D. C.; McKelvey, J. M., Jr.; Sullivan, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 4261 and references cited therein.
(17) de la Mare, P. B. D. *Acc. Chem. Res.* **1974**, *7*, 361.
(18) Fyfe, C. A.; Van Veen, L., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 3366.
(19) Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830. Tee, O. S.; Paventi, M. *Can. J. Chem.* **1983**, *61*, 2556.
(20) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.

Table I. Constants for the Reaction of Bromine with Salicylic Acid (1), Methyl Salicylate (6), and *o*-Anisic Acid (7)[a]

	1	6	7
k_2	~4700[b]	610	180
k_2'	3.3×10^6		8600
k_2''		7.2×10^9	
pK_1	2.88		3.99
	(2.98)[c]		(4.08)[d]
pK_2	(13.61)[c]	(9.87)[c]	

[a] At 25 °C, I = 0.11 M. Units of ks are M^{-1} s^{-1}. Values of pK in parentheses are from the literature; the others are from fitting. [b] See ref 23. [c] Reference 4. [d] Reference 5.

constants (k_2^{obsd}; Tables S1, S2, supplementary material) have been corrected[2,19] for the actual concentration of free bromine in solution.[21] Their variations with acidity are displayed as pH–log k_2^{obsd} profiles in Figures 1 and 2.

For methyl salicylate (**6**) the variation of k_2^{obsd} with pH is similar to that found for other simple phenols.[2,3,8,9] Its pH–rate profile, shown in Figure 1, can be generated from eq 1 in which k_2 is the rate constant for bromine attack on the undissociated substrate, k_2'' is for reaction on the anion, and K_2 is the acid dissociation constant of the phenolic pH of the substrate (see eq 2). The fitted values

$$k_2^{obsd} = k_2 + k_2''k_2/[H^+] \quad (2)$$

of k_2 and k_2'', which are given in Table I, are comparable to those found for other phenols and their anions.[2,3,8,9]

The pH–rate profile for *o*-anisic acid (**7**) (Figure 1) is attributed to reaction upon the free acid at low pH and upon the anion at pH >1.5. It can be represented by eq 3 where k_2 is the rate constant for bromine attack on the

$$k_2^{obsd} = \frac{(k_2[H^+] + k_2'K_1)}{(K_1 + [H^+])} \quad (3)$$

free acid, k_2' is for attack on its anion, and K_1 is the ionization constant for the COOH group. Fitted values of k_2, k_2', and K_1 (expressed as pK_1) are presented in Table I. There is good agreement between the fitted value of pK_1 (3.99) and the literature value (4.08).

Figure 1 also shows the pH–rate profile for the attack of bromine on salicylic acid (**1**).[22] It can also be represented by eq 3 by using the appropriate constants given in Table I although the data at low pH show insufficient leveling off to define k_2 accurately.[23] Again, there is good agreement between the fitted and the literature values of pK_1 (2.88 and 2.98), bearing in mind that in the present work I = 0.11 M.

Figure 2 shows the pH–rate profiles obtained for various 4- and 5-substituted salicylic acids. They show no significant tendency to level off at low pH, and so the k_2 term in eq 3 may be dropped, as in eq 4. 5-formyl and 5-nitro

$$k_2^{obsd} = k_2'K_1/(K_1 + [H^+]) \quad (4)$$

Table II. Constants for the Attack of Bromine on Substituted Salicylic Acids in Aqueous Solution[a]

substrate (**8** or **9**)	k_2'	pK_1 fitted	pK_1 lit.
5-Me (**8a**)	2.1×10^6	3.08	3.02[b]
5-CHO (**8b**)	3.8×10^5	2.76	[c]
5-Br (**8c**)	2.0×10^5	2.68	2.62[d]
5-SO_3^- (**8d**)	9.2×10^4	2.62	2.62[e]
5-NO_2 (**8e**)	1.7×10^4	2.10	2.05[d]
4-Me (**9a**)	~4.2×10^7[f]	3.13[g]	3.13[b]
4-Cl (**9b**)	1.4×10^6	2.58	[c]

[a] Parameters used to generate rate profiles by using eq 4 or 5. Units of k_2' are M^{-1} s^{-1}. At 25 °C, I = 0.11 M. [b] Reference 24b. [c] Not available. [d] Reference 24a. [e] Reference 4. [f] Poorly defined by the limited rate profile (Figure 2). [g] Assumed.

derivative (**8b** and **8e**) values of k_2^{obsd} show a further increase above pH 5, which is ascribed to the onset of reaction on the corresponding dianions; it can be accomodated by using eq 5. This type of behavior, which was

$$k_2^{obsd} = \frac{k_2'K_1}{(K_1 + [H^+])} + \frac{k_2''K_2}{[H^+]} \quad (5)$$

observed previously for *p*-hydroxybenzoic acid,[3] is not seen for most of the salicylic acids because their second ionizations are so difficult[4,24b] (see the introduction). 4-Methylsalicylic acid (**9a**) is so reactive that its rate of bromination could be measured only at pH <3, and so its pH–rate profile is incomplete (Figure 2). Values of k_2' and pK_1 for the various derivatives (**8** and **9**) are collected in Table II. The latter values show very good agreement with those from the literature, where available.

For salicylic acid the rate data in the plateau region of the rate profile (Figure 1) show more scatter than elsewhere. This may be due to the rates approaching the limits of the stopped-flow equipment and to using lower concentrations of substrate (0.1 mM) and the bromine (0.01 mM) to offset this. Nevertheless, we considered that traces of metal ions[25] might be contributing to the scatter since salicylate ions form complexes of transition-metal ions.[26] However, adding ferrous ion or cupric ion (0.01 mM) at pH 3.9 or 4.7 we obtained values of k_2^{obsd} within the spread of the values for the plateau region measured in the absence of these ions. It seems, therefore, that the scatter is simply due to approaching the limits of the instrumentation.

As a possible probe of intramolecular proton transfer concerted with bromine attack (**2** → **5** in one step, Scheme I) we also measured rates of bromination in D_2O. In this medium a deuteron would be transferred, and a rate reduction should be observed. Because of the problem of scatter in the data of **1**, just discussed, experiments were carried out with the slower reacting 5-bromo derivatives **8c** in the region of the plateau in its rate profile. For the pH (pD) range 4–6 the average value of k_2^{obsd} in H_2O was 2.14×10^5 M^{-1} s^{-1} (4 pH values) and 1.30×10^5 M^{-1} s^{-1} (6 pD values) in D_2O. From these the solvent isotope effect is 1.65. For comparison we also measured the effect of D_2O on the bromination of *o*-anisic acid (**7**). At pH (pD) 5.5, where **7** reacts via its anion (Figure 1), the observed solvent isotope effect was 1.37.

(21) The second-order rate constants are calculated as though bromine is the only significant electrophile, as has been shown for phenols.[8] With some phenoxide ions, however, tribromide ion makes a contribution.[2,8] This is probably the case for those of the present substrates where reaction via the phenoxide ion is indicated. Our neglect of this minor pathway should not, however, affect our major mechanistic conclusions.

(22) The rate of bromination of salicylic acid in water has been measured once before (Rao, T. S.; Mali, S. I. *J. Prakt. Chem.* **1974**, *316*, 1047), by using a continuous-flow method with an electrochemical probe. However, the medium used (0.002 M KCl) was unbuffered, and so the reported value of k_2^{obsd} = 4.2×10^5 M^{-1} s^{-1} cannot easily be compared to the present results.

(23) The value of k_2 for **1** may be slightly elevated since any upward trend in the data due to ionic strength effects at pH <1 will be incorporated into it. However, we note that fitting eq 4, rather than eq 3, to the data gives a poorer value of pK_1 (2.80), further from the literature value of 2.98.[4]

(24) (a) "Dictionary or Organic Compounds", 4th ed.; Eyre & Spottiswoode: London, 1965; Vol. I. (b) Chattopadhyaya, M. C.; Singh, R. S. *Indian J. Chem., Sect. A* **1980**, *19A*, 141.

(25) As suggested to us by Dr. M. F. Powell, the most probable source of metal ions is the KBr since the water used was deionized and distilled from glass.

(26) "Stability Complexes of Metal Ion Complexes"; Chemical Society: London, 1964; Spec. Publ.–Chem. Soc. No. 17.

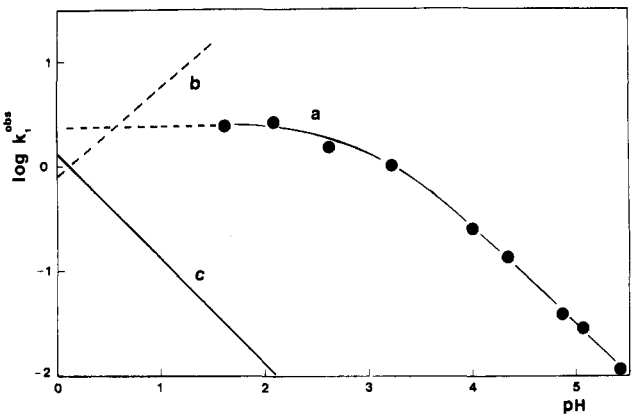
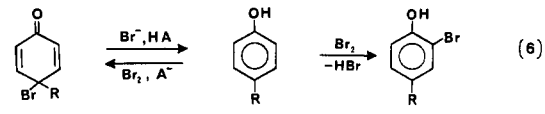


Figure 3. (a) pH–rate profile for the debromination of the ipso dienone **13** derived from 5-methylsalicylic acid (**8a**) in 0.1 M aqueous KBr. (b) pH dependence of the pseudo-first-order rate constant for bromine attack on **8a** under the conditions employed for the measurement of profile a. (c) pH dependence of the pseudo-first-order rate constant for the debromination of the ipso dienone **11** (R = Me) derived from *p*-cresol, also in 0.1 M aqueous KBr.[1a]

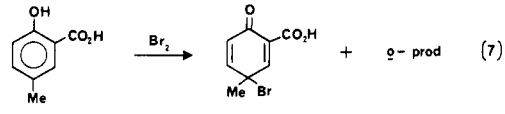
As noted earlier, we tried to observe the transient cyclohexadienone **5** (Scheme I) without success. However, we were able to observe the cyclohexadienone resulting from bromine attack ipso to the methyl group of 5-methylsalicylic acid (**8a**). Several such "ipso dienones" formed from *p*-alkylphenols (eq 6) have been studied in this laboratory.[1a,27] The initial fast reaction of bromine with the alkylphenol **10** is partitioned between ortho attack (~90%) and ipso attack (~10%). The former leads



11 10 12

quickly to ortho products whereas the latter gives the observable dienone **11** which undergoes relatively slow decomposition by debromination.[1a] This process is induced by Br^- and is catalyzed by H^+ [1a] *and* by buffer acids.[27a] In the present work we have found comparable behavior using 5-methylsalicylic acid (**8a**) as the substrate.

Bromine reacts rapidly with the anion of **8a** (Figure 2 and Table II) to produce a transient absorption at ~250 nm[1] which is attributed to the ipso dienone **13** (eq 7). At



8a 13

fixed pH and $[Br^-]$ the decay of this absorption follows first-order kinetics and the rate constants (k_1^{obsd}) vary with pH as shown in Figure 3; the actual data are given in Table S3 (supplementary material). Kinetic studies could not be carried at pH <1.5 because the rate of bromine attack is slower in this region (Figure 3). As found with other ipso dienones,[1a,27] the extent of the absorbance change for the decay of **13** is about 10% of that expected if all of the bromine was converted to **13**, and so we estimate that only ~10% of the initial bromine attack is ipso.

The form of the rate profile ascribed to **13** (Figure 3) is, of course, kinetically ambiguous. It could be due to a reaction of the free acid form (eq 8) or to a proton-catalyzed reaction of the conjugate anion (eq 9). former case

$$k_1^{obsd} = k_1[H^+]/(K_1 + [H^+]) \quad (8)$$

$$k_1^{obsd} = k_2K_1[H^+]/(K_1 + [H^+]) \quad (9)$$

(eq 8) the fitted value of k_1 is 2.59 s^{-1}, and for the latter k_2 is 3010 M^{-1} s^{-1}. In both cases the fitted value of pK_1 for **13** is 3.06, which is reasonable for the assigned dienone structure. The choice between the two mechanistic possibilities is deferred to the Discussion section.

One further point concerning the behavior of **13**: we find no evidence of buffer catalysis in its decomposition. In contrast, the ipso dienone **11** (R = Me) derived from *p*-cresol shows significant general acid catalysis.[27a]

Discussion

The value of σ^+ normally cited for m-CO_2^- is –0.028,[28] very close to 0, although a better value may be 0.10.[3] Therefore, one expects the reactivity of a salicylate anion to be very close to or less than that of the analogous phenol which lacks the carboxylate moiety. From the present study the rate constant for the attack of bromine on the unsubstituted ion **2** is 3.3×10^6 M^{-1} s^{-1}, whereas that for phenol is[1a,2] 4.2×10^5 M^{-1} s^{-1}. This difference in reactivity, a factor of 7.9, is relatively small, but much larger differences are evident for the less reactive salicylate ions: for the 5-nitro anion k_2' is 1.7×10^4 M^{-1} s^{-1}, whereas k_2 for *p*-nitrophenol[27b,29] is <60 M^{-1} s^{-1}, a factor of >2800.

The differences in reactivity toward bromine between salicylate ions and phenols can be expressed more succintly with Hammett plots. The values of k_2' for the 5-substituted derivatives in Table II give a reasonable plot (r = 0.92, 5 points) with $\rho^+ = -2.69$. This is in marked contrast to a series of para-substituted phenols for which $\rho^+ = -5.21$ (r = 0.98, 7 points).[3,30] Clearly, the salicylate ions show a greatly reduced sensitivity to substituent change, which suggests that the *o*-carboxylate group is significantly modifying "normal" phenol reactivity.

The reactivity of salicylate ion (**2**) can also be compared to that of the anion of *o*-anisic acid (**7**). This comparison has the advantage that it is not dependent on the choice of a value of σ^+ for m-CO_2^-.[31] From the values of k_2' in Table I the anion **2** is 380 times as reactive as the anion of **7** toward bromine. This ratio is high since phenol[1a] is only 12 times as reactive as anisole,[32] and it supports the idea that **2** is showing some enhanced reactivity.

In addition to *o*-anisic acid, we also studied methyl salicylate (**6**) as a model compound. The value of k_2 for reaction of its undissociated form is similar to that for ethyl *p*-hydroxybenzoate,[3] as one expects. The corresponding k_2 for salicylic acid is ~8 times higher but its value is not well defined by the available data (Figure 1).[23]

The rate constant for reaction of the anion of methyl salicylate (k_2'', Table I) is at the diffusion-controlled limit,[33]

(27) (a) Tee, O. S.; Iyengar, N. R.; Bennett, J. M., manuscript in preparation. (b) Bennett, J. M., unpublished results.

(28) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions", Wiley: New York, 1963.

(29) From a few experiments in dilute $HClO_4$ solution Kulic and Vecera[9] estimated k_2 for *p*-nitrophenol to be 110 M^{-1} s^{-1}. However, we have determined the rate profile from pH 0–4 and have found it to be strictly linear (slope = +1), indicating reaction on the anion only in this range.[27b] From our data k_2 is <60 M^{-1} s^{-1}.

(30) Kulic and Vecera have a similar value of $\rho^+ = -5.0$.[9]

(31) As discussed previously,[3] the value of –0.028[28] does not fit well for *o*-anisate, *p*-anisate, and 2-furoate. A better value for these substrates appears to be +0.10, which essentially equals σ_m based on the substituted benzoic acid ionization.[3]

(32) Aaron, J. J.; Dubois, J. E. *Bull. Soc. Chim. Fr.* **1971**, 603.

(33) Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

as is typical for monosubstituted phenoxide ions.[2,3,8,9] It provides a useful guide to the reactivity of the *o*-carboxyphenoxide ion **2′**. The attack of bromine on this ion is probably also diffusion controlled although it is possible that its rate is slightly reduced due to a stabilizing effect of the internal hydrogen bond. In any event, an appropriate value of the rate constant for bromine attack on **2′** (k_2''', eq 10) is $\leq 7 \times 10^7$ M^{-1} s^{-1}.

$$2 \underset{K_1}{\overset{H^+}{\rightleftharpoons}} 1 \underset{H^+}{\overset{K_3}{\rightleftharpoons}} 2' \xrightarrow[Br_2]{k_2'''} \quad (10)$$

If salicylate ion **2** reacts via its minor tautomer **2′** (Scheme I and eq 10) the rate constant for the plateau region of the rate profile (previously evaluated as k_2') is given by eq 11. In this case the variation of k_2' with

$$k_2' = k_2'''K_3/K_1 \quad (11)$$

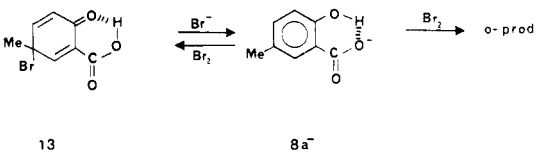
substituent depends on the ρ values for the individual constants on the right side of eq 11. As discussed above, the constant k_2''' is probably very close to diffusion controlled and so it should have $\rho^+ \sim 0$.[2] The constant K_3 is for the ionization of the phenolic OH of **1** and so one expects its ρ to be ~ 2.2.[34] For a series of 17 salicylic acids values of K_1 give $\rho = 0.89$.[35] Overall, these considerations require that k_2' in eq 11 has a $\rho^+ \sim +1.3$. The *positive* value indicates that electron-withdrawing groups should *increase* the apparent reactivity of salicylate ions, as was found for *p*-hydroxybenzoate ions,[3] but the present data for salicylate ions yield $\rho^+ = -2.7$. For this value to be accommodated by the model represented by eq 10/ and 11 would require very unusual ρ values for k_2''' and/or K_3.

Another line of argument militates against the pathway involving **2′**. If k_2''' has the value of 7×10^9 M^{-1} s^{-1}, as discussed above, the observed value of k_2' requires that $K_3 = 4.9 \times 10^{-7}$ M and $pK_3 = 6.31$. This pK seems quite low for **1** ionizing to **2′**, particularly since the pK_a of methyl salicylate is 9.87. Furthermore, if k_2''' is less than diffusion controlled then pK_3 would have to be *lower* still.

On the basis of the previous two paragraphs we reject the pathway involving the tautomeric ion **2′** (pathway b Scheme I, and eq 10). We also feel that pathway a (Scheme I) via the protonated dienone **4** is unlikely for the reasons given in the introduction and because of the observed value of ρ^+. For para-substituted phenols and anisoles the respective values of ρ^+ for aqueous bromination are −5.21[3] and −6.54.[32] Accordingly, a similar value would be expected for pathway a since it also involves the rate-limiting formation of a cationic intermediate. Stabilization of **4** by internal hydrogen bonding should make ρ^+ less negative. However, the observed value of −2.7 is *much less* negative and seems more appropriate to pathway c (Scheme I) in which intramolecular (asynchronous?)[36] proton transfer limits the build-up of positive charge.

We also measured solvent isotope effects in the hope that they might add weight to these arguments. For the *o*-anisate ion, reaction in D_2O reduced the rate by a factor of 1.37. This value is presumably an effect operating on the bromide ion leaving group since similar values (1.2–1.4) have been found for solvolyses[37] and for alkene and alkyne brominations.[38] The value of 1.65 obtained for 5-bromosalicylate ion is higher, but not dramatically so. Part of it must be due to an effect on incipient Br^- and the remainder to a proton in flight at the transition state. We note that low solvent isotope effects are common in reactions involving intramolecular proton transfer.[39] Accordingly, the observed effects of 1.65 is not inconsistent with pathway c, but it is not really large enough to constitute substantial evidence.

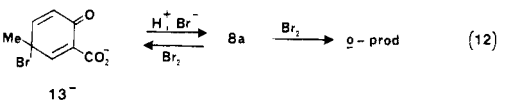
Scheme II



13 **8a⁻**

Much stronger support for pathway c is afforded by the behavior of the ipso dienone **13** generated from 5-methylsalicylic acid (**8a**) (eq 7). The form of the rate profile for its decay (Figure 3) may be represented equally well by eq 8 or 9. The former equation corresponds to a reaction of the undissociated form of **13** and the latter to an acid-catalyzed reaction of its anion (**13⁻**). Of these two possibilities, we believe that first is more likely for the reasons given below.

For the ipso dienone **11** (R = Me) (eq 6) the second-order rate constant (k_2) for decomposition in 0.1 M aqueous KBr is 1.3 M^{-1} s^{-1} (Figure 3, c).[1a] If the dienone **13** reacts via its anion (**13⁻**, eq 12), the analogous value of k_2 is *2300 times larger*. This is unreasonable for the effect



13⁻ (12)

of the substituent *m*-CO_2^- on the processes depicted in eq 6 and 12. As remarked earlier, the value of σ_m for *m*-CO_2^- is ~ 0 and so essentially no substituent effect would be expected. There might be a modest electrostatic effect (factor of ~ 10)[6a,7,40] due to the negative charge of **13⁻** facilitating the approach of H_3O^+ but this would be offset by an inhibitory effect on the approach of Br^-. A factor of 2300 ($\Delta\Delta G^\ddagger = 4.6$ kcal/mol) also appears large for hydrogen-bond stabilization of the protonated form of **13⁻**. Furthermore, if **13** reacted via **13⁻**, one would expect to observe general acid catalysis, as found for **11** (R = Me),[27a] but *no such catalysis was found.*

In view of the foregoing, it seems more probably that **13** reacts as such and that its carboxyl group functions as an *intramolecular* general acid (Scheme II). This compliments the behavior of the dienone **11** (R = Me), whose decomposition is catalyzed by *external* general acids.[27a] Note, however, that in **13** → **8a⁻** the attack for Br^- and internal proton transfer are not necessarily synchronous.

For the intramolecular process shown in Scheme II we can estimate the effective molarity (EM)[41] of the internal carboxyl catalyst of **13**. The breakdown of **11** (R = Me) has a Brønsted $\alpha \sim 0.27$,[27a] and for an acid of $pK_a = 3.06$, as found for **13**, the predicted k_2 in 0.1 M aqueous KBr is 0.045 M^{-1} s^{-1}. However, for **13** we have $k_1 = 2.59$ s^{-1} and so EM = 58 M. This value is modest, as has usually been found for intramolecular general acid catalysis.[41]

It is proposed, then, that the carboxyl group of **13** catalyzes the debromination of **13** by bromide ion (**13** → **8a⁻**, Scheme II). By the principle of microscopic reversibility

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(35) Dunn, G. E.; Kung, F. L. *Can. J. Chem.* **1966**, *44*, 1261.
(36) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.
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(41) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

it follows that the carboxylate moiety of $8a^-$ catalyzes the ipso attack of bromine in the reverse reaction which forms **13** (Scheme II). This process is completely analogous to pathway c in Scheme II and it provides additional support for the existence of this type of pathway for salicylate ions, in general.

Our results have implications with respect to the reasons why the hydroxyl group is so good at facilitating cation-forming reactions.[42] Usually, it is attributed to overlap between an oxygen lone pair and the incipient (delocalized) cation (e.g., as in **4**, Scheme I). However, since HO is a much better electron-donor than MeO ($\sigma_p^+ = -0.92$ vs. -0.778),[28,43] it has been argued that hydroxyl may interact differently. In particular, it has been suggested that there is hyperconjugative release from the O–H bond toward the cationic center.[42,44] For this to occur the O–H bond must lie in a plane parallel to the p orbitals of the incipient cation. In salicylate ions, such as studied here, the O–H bond is held by a hydrogen bond in a plane perpendicular to that required for hyperconjugation. Thus, if hyperconjugative release was of prime importance in determining the reactivity of phenols toward electrophiles, salicylate ions should be *less* reactive than phenols, contrary to the present findings.

The other explanation given for the superior electron-donating ability of hydroxyl over methoxyl[43] is that the O–H bond is stretched in the reaction transition state.[42] In extreme cases the OH bond may actually be broken in the rate-limiting step and this may be the case for the salicylate ions studied here. The present results raise the possibility that the attack of electrophiles on phenols (and enols) may be subject to general base catalysis. Ongoing studies in this laboratory are concerned with this possibility.

Experimental Section

Materials. Salicylic acid (Fisher Scientific) and 5-bromosalicylic acid (Aldrich) were recrystallized from water before use. The remaining substrates were from Aldrich, except for methyl salicylate (May and Baker), 5-sulfosalicylic acid (J. T. Baker), and 5-nitrosalicylic acid (Fluka). They were used as received. All reagents, buffer acids, etc. were of the highest grade available.

Kinetic Methods. All kinetics solutions were 0.1 M in aqueous KBr. Normally the total ionic strength $I = 0.11$ M, due to KBr + buffer. At higher acidities (pH <2), where dilute HCl solutions were used, I = [KBr] + [HCl]. For such solutions pH was calculated from [HCl] by using an activity correction of the ionic strength based on the Davies equation.[45] Buffer solutions (I = 0.01 M) were made from the tables given by Perrin for chloracetate, acetate, succinate, and phosphate.[46] Bromine solutions were made by dilution of a fresh stock solution in aqueous KBr, made up by weight.

Kinetics experiments were carried out at 25.0 ± 0.1 °C using the stopped-flow apparatus,[47] data acquisition system,[20] and data analysis methods[19] described previously. Rates of bromine attack were measured as the decrease in the tribromide ion band at 275 nm under pseudo-first-order conditions (10-fold or more excess of substrate). Normally, $[substrate]_0 = 0.5$ mM and $[Br_2]_0 = 0.05$ mM, except for the fastest reactions, where these concentrations were reduced by a factor of 5. First-order rate constants were converted to second-order rate constants (k_2^{obsd} in Table S1, S2, supplementary material) taking into account the substrate concentration and the concentration of free bromine.[19]

Decomposition of the ipso dienone **13** derived from 5-methylsalicylic acid **8a** was monitored as a decrease in absorbance at 250 nm. The dienone was generated in situ in the stopped-flow apparatus by mixing a 0.5 mM (1 mM at pH <3) solution of **8a** with 0.1 mM bromine, both solutions being 0.1 M in KBr and in a suitable buffer. Below pH 1.5 biphasic kinetics were observed due to the rate of bromine attack (which generates **13**) becoming comparable to the rate of decomposition of **13** (see Figure 3). From the absorbance changes pseudo-first-order rate constants (k_1^{obsd}) were obtained which were independent of the concentrations of the substrate or bromine but which vary with [Br^-] and with pH (Figure 3). This behavior is analogous to that found for other ipso dienones derived from *p*-alkylphenols.[1a,27]

Products. Bromination of salicylic acid (in buffer pH 4.5), *o*-anisic acid (in dilute H_2SO_4), and methyl salicylate (in dilute H_2SO_4) gave the expected 5-bromo derivatives in high yield. Similarly, bromination of 5-bromosalicylic acid gave 3,5-dibromosalicylic acid and not 2,4-dibromophenol, which would be the product of bromodecarboxylation.

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Registry No. **1**, 69-72-7; **6**, 119-36-8; **7**, 579-75-9; **8a**, 89-56-5; **8b**, 616-76-2; **8c**, 89-55-4; **8d**, 46326-08-3; **8e**, 96-97-9; **9a**, 50-85-1; **9b**, 5106-98-9.

Supplementary Material Available: Rate constants for the reaction of bromine with **1**, **6**, **7**, **8**, and **9** (Tables S1, S2) and for the decomposition of **13** (Table S3) (5 pages). Ordering information is given on any current masthead page.

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(43) This is only true in solution. In the gas phase MeO is better at stabilizing cations than is HO. See, for example: Holmes, J. L.; Lossing, F. P. *Can. J. Chem.* **1982**, *60*, 2365.

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