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Mechanisms Of The Aqueous Bromination Of p-Hydroxybenzoic Acid, Salicylic Acid And Phenol.

N. Rani Iyengar

A Thesis

in

The Department

of

Chemistry

Presented in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy at
Concordia University
Montréal, Québec, Canada

May 1985

ABSTRACT

Mechanisms Of The Aqueous Bromination Of p-Hydroxybenzoic Acid, Salicylic Acid And Phenol.

"N. Rani Iyengar, Ph.D."
Concordia University, 1985

The kinetics of aqueous bromination of p-hydroxybenzoic acids and salicylic acids have been studied and novel mechanistic conclusions have been reached. In the aqueous bromination of phenols cyclohexadienone intermediates have been observed for the first time and the enolization of these intermediates has been studied in detail.

The anions of p-hydroxybenzoic acid and its 3-bromo derivative react faster with bromine than anticipated. This is due to reaction via the minor tautomeric form (a p- carboxyphenoxide ion).

The bromination of the salicylate ions probably occurs via a concerted pathway in which the attack of bromine and an intramolecular proton transfer (from OH to carboxyl) occur simultaneously. Support for this pathway arises from the behaviour of the ipso-dienone derived from

5-methylsalicylic acid. In the debromination of this ipso-dienone the carboxyl group functions as an intramolecular general acid catalyst. The reverse reaction, formation of the ipso-dienone, must be catalyzed by the carboxylate group, which is analogous to the concerted pathway.

The enolization of 4-bromo-2,5-cyclohexadienone in the pH range of 0-6 is catalyzed by acid and water. Buffer catalysis studies indicate the reaction to be general base-catalyzed and general acid-catalyzed. The former is explained by the rate limiting proton abstraction from the cyclohexadienone and the latter is attributed to a termolecular transition state (H_2O.dienone.HA).

In the bromination of p-alkylphenols 10% bromine attack occurs ipso to the alkyl group resulting in ipso-dienones. These undergo debromination to reform the substrate and the reaction is general acid-catalyzed and bromide ion dependent. The ipso-dienone from 5-methyl-salicylic acid undergoes fast debromination which is ascribed to intramolecular general acid catalysis.

Buffer catalysis studies for the bromination of phenol indicate that the formation of the cyclohexadienones is general base-catalyzed.

To My Parents

ACKNOWLEDGEMENTS

I wish to thank Dr. O.S. Tee for his guidance and the keen interest he has shown throughout this work. I will always be indebted to him for his assistance, patience and moral support.

Furthermore, I would like to thank the following:

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Finally all my fellow graduate students for their friendship.

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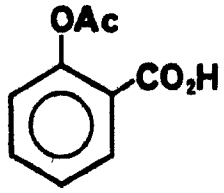
CHAPTER 1

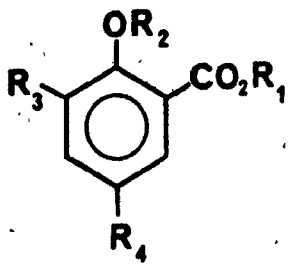
General Introduction

Salicylates have been used as drugs since antiquity. The name "Salicylate" is derived from the Latin "Salix" for the willow, a tree which grows near water. The use of preparations extracted from the leaves, barks and fruits of plants containing methyl salicylate is as old as herbal therapy, itself. Today, aspirin rates next to alcohol as being the most consumed drug in the world. Actual demand for this drug is around 70 million kilograms.[1]



Aspirin

Most of the naturally occurring salicylates, including salicylic acid itself, are therapeutically effective as weak anti-inflammatory, analgesic and/or anti-pyretic agents, although some of them are less potent than aspirin.[1] Some of the principal salicylates used as analgesic, anti-inflammatory, anti-pyretic, anti-thrombic are:[1]



R_1	R_2	R_3	R_4
H	H	H	H
H	Ac	H	H
H	H	H	Cl
H	H	OH	H
H	Ac	OAc	H
Me	H	H	H
H	H	Me	H
Ph	H	H	H

Some of the derivatives of aspirin have specific biological properties and can be used as unique therapeutic agents, e.g. 3,5-dibromo aspirin is used as an anti-sickling agent.[2] The 3,5-dibromosalicylic acid is used as a bactericide.[107] From a recent article by Sorenson[106] it is clear that copper complexes of salicylic acid can be used as effective anticonvulsants and also that copper salicylates with superoxide dismutating reactivity act as retarding agents for tumour grpwth in mice.

Many simple derivatives of the basic salicylate structure have been and still continue to be developed because these natural drugs have been so successful historically. Even in the present day, they still present a safe and effective group of compounds for therapy.

There is wide interest in research work regarding the biosynthesis of the salicylates in plants and microorganisms. This interest is not only due to the biological importance but also since the research may provide practical means for obtaining these compounds as raw materials for the synthesis of more elaborate derivatives of this group of drugs.[1] The action of salicylates on vital enzyme systems is a much-studied biochemical research problem.

Salicylates have toxic side-effects which include, acute salicylate poisoning in infants, disturbance of the acid-base equilibrium and gastrointestinal bleeding. Research is currently being carried out to gain better insight into the causes and treatments of these unwanted side-effects.[1]

Phenol and its derivatives are chemicals of great industrial and biochemical significance. As a result an understanding of the chemistry of these compounds has con-

siderable practical as well as theoretical value. Industrial applications include the use of phenols in the production of insecticides, fungicides, antiseptics, disinfectants, dyes and polymers.[3] They are also added as oxidation inhibitors to motor fuels, oils and edible oils.[3] An unknown amount of chlorophenols is released into the environment by chlorination of drinking water containing phenols from various industrial sources.[4] Effluents from paper and pulp industry are known to contain toxic components.[5] Some of these compounds have been identified as chlorinated phenols, guaicols, catechols and trihydroxybenzenes.[6,7] These wastes must be suitably treated in order to eliminate phenols.

Phenols are also important in biochemical processes. Many substituted phenols behave as chemical inhibitors and therefore are widely used in chemotherapy. In addition, biochemicals such as catecholamines and tannins contain phenol or polyphenol components. Theoretical studies often use phenols or polyphenols as suitable models for these more complex molecules.[8]

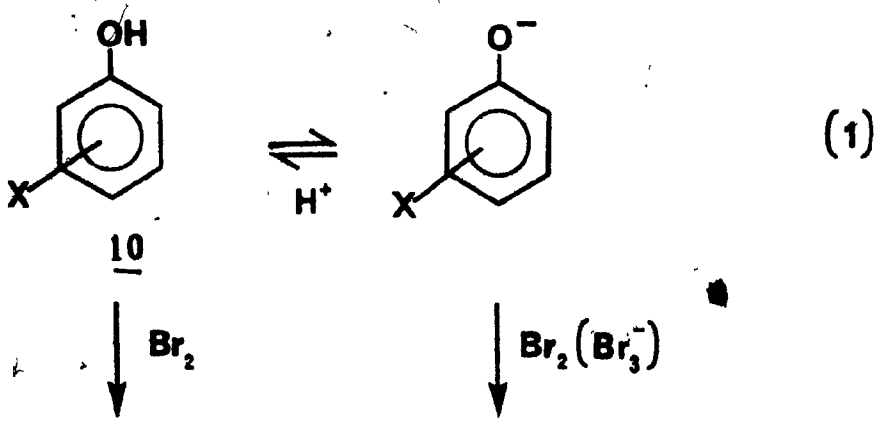
The work in this thesis deals with the mechanisms of bromination of salicylic acid, p-hydroxybenzoic acid and their derivatives, and of various phenols. The salicylic acid monoanion has an intramolecular hydrogen-bond and a

comparative kinetic study should make it possible to assess the effect of this hydrogen-bond on the ease and mechanism of electrophilic attack.

Electrophilic substitution reactions of phenols are usually presumed to involve the formation of cyclohexadienone intermediates. In the present work such intermediates have been observed for the first time in the aqueous bromination of simple phenols.

Bromination of Phenols:

This reaction has been investigated by various research groups using acetic acid as solvent. The rate of bromination of phenol in anhydrous acetic acid relative to that of benzene has been determined by de la Mare and his coworkers.[14] Also the reaction has been studied for various alkyl phenols in the presence of LiBr and $LiClO_4$ by de la Mare et al.[17] Bell and Rawlinson[9] have shown that phenols in dilute aqueous perchloric acid solution contain two respective species: the molecule itself and the phenoxide ion. Both of these species were observed to react with molecular bromine and reaction between the phenoxide ion and tribromide ion was also observed[9] (equation 1).



10 (1)

The main draw back of the study[9] is, it is limited to two pH units and as the reactions are fast they mention that the rate constant for bromination of phenol is of low accuracy and the rate constant for the bromination of phenoxide ion was not measured.

Kulic and Vecera[11] have studied the bromination of p-substituted phenols, also in dilute aqueous perchloric acid media. They reported the rate constants for the phenol and phenolate brominations. Correlation of log k values with σ^- constants for bromination of both phenols and phenolate anions indicate that bromination of phenol is more selective than that of phenolate ions.

Paventi[10] recently studied the same reaction in

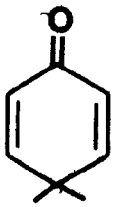
aqueous solutions, pH 0 - 7. As observed by the earlier workers, Paventi also has shown that the bromination of phenol is overall second-order: first-order in phenol and first-order in bromine. The reaction yields o- and p-bromo isomers, the p-isomer being the major product. The rate constant reported for the reaction of phenol with bromine was $4.2 \times 10^{3}\ M^{-1}\ s^{-1}$ which is slightly higher than the value reported by Bell,[9] which was admitted to be of low accuracy. The rate constant observed for the bromination of phenoxide ion is $2.2 \times 10^{10}\ M^{-1}\ s^{-1}$. This value is high, but is complicated by polybromination and is due to the weighted sum of the reactivity of free bromine and tribromide ion.[10] Overall the results of Paventi seem to be better as they were obtained from more reliable methods and over a wide range of pH.

Dienones:

In reactions of phenols the formation of cyclohexadienones as intermediates has often been postulated. The phenol-cyclohexadienone rearrangement can be explained as a tautomeric change in phenols. This simple tautomerism in phenols has not been observed earlier in simple phenols without any substituents. The cyclohexadienones reported

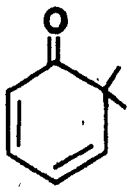
have been for the electrophilic substitution reactions with 4-, 2,4-, and 2,6-alkyl substituted phenols, only.[12,14,18-25]

Stable cyclohexadienones were detected in dilute solutions by spectroscopic methods in the bromination of 2,6-dialkylphenols. Ershov and his co-workers[12] had isolated the cyclohexadienone of 2,6-di-t-butylphenol in bromination reactions. Cyclohexadienones can exist in two isomeric forms p-dienones (2,5-cyclohexadienone) and o-dienone (3,5-cyclohexadienone).



2,5-Cyclohexadienone

(p-Dienone)



3,5-Cyclohexadienone

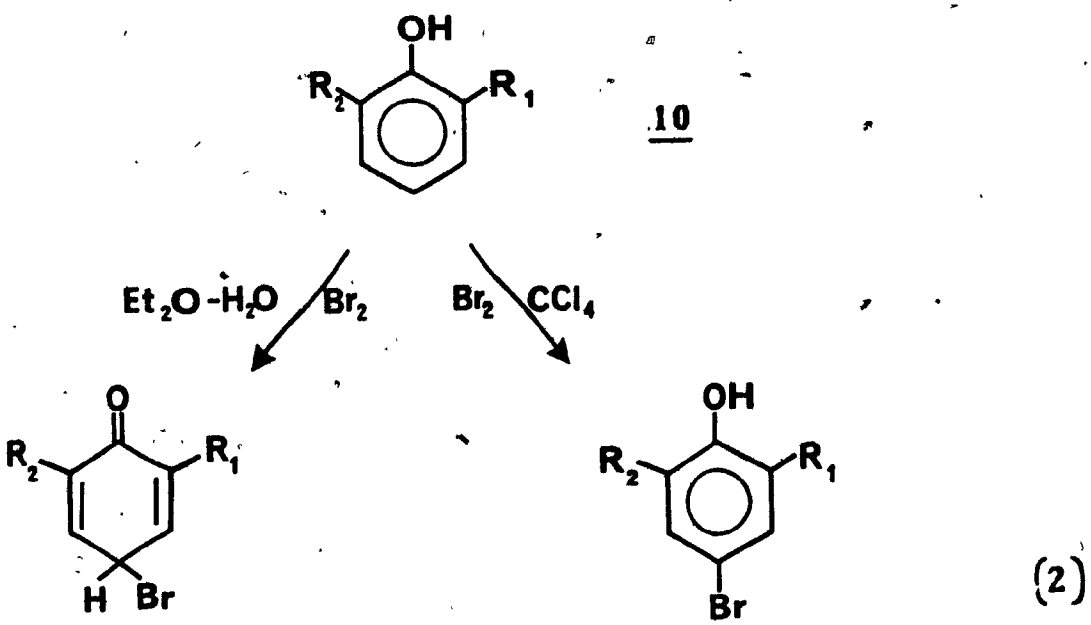
(o-Dienone)

The formation of o- or p-dienone or both as intermediates depends on the position of substituents in the substrate phenol. If a p-substituted phenol is brominated, the major o-bromo product is formed via the o-dienone and in the case of 2,6-disubstituted phenols, a p-bromo product is formed via the p-dienone. The ease of the phenol-dienone rearrangement increases with the increasing steric hindrance

of the phenolic hydroxyl,[3] i.e.with bulky substituents on 2,6-positions of the phenol. This is because the bulky substituents on 2- and 6-positions hinder the hydroxyl group, disturbing the co-planarity between the hydroxyl and aromatic ring, and also inhibit the hydrogen-bond formation between phenol molecules. It has been shown by spectroscopic methods that there are absolutely no hydrogen-bonds in 2,6-di-t-butylphenol.

Ershov and Volod'kin have also reported the requirement of the presence of a substance possessing proton-acceptor properties (ether, dioxane, water, pyridine etc.) for the formation of stable cyclohexadienone type intermediates. The influence of proton acceptor is very clearly exhibited in the bromination of 2,6-dialkyl phenols. In polar solvents (ether-water) good yields of the cyclohexadienone intermediate were obtained whereas in non-polar solvents (CCl_4) the product 4-bromo- 2,6-dialkylphenol was formed immediately (equation 2).

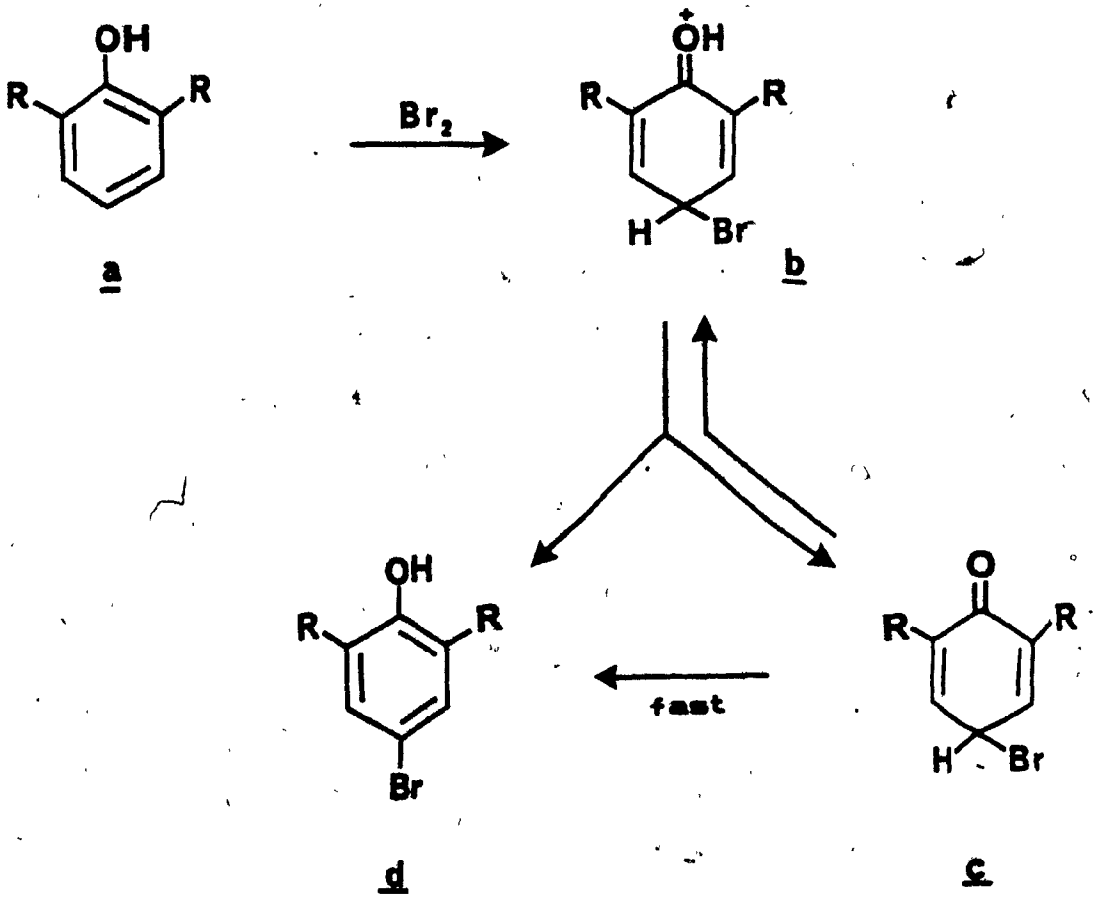
Dienone intermediates have also been observed in the nitration of 2,6-dialkylphenols but they have been less thoroughly investigated due to the complexity of the reaction.



In cases where there is an ipso-attack of the electrophile, elimination of proton does not lead to an aromatic structure, instead there is either a migration of the substituent in the ring or an elimination of the electrophile to give back the substrate.

From the research work of de la Mare et al in this area it is evident that cyclohexadienone intermediate enolizes to form the product. They had studied the enolization of the cyclohexadienone intermediate of 2,6-di-t-butylphenol (Scheme 1) in acetic acid and aqueous acetic acid media.[14,18] Under acidic conditions the rearrangement

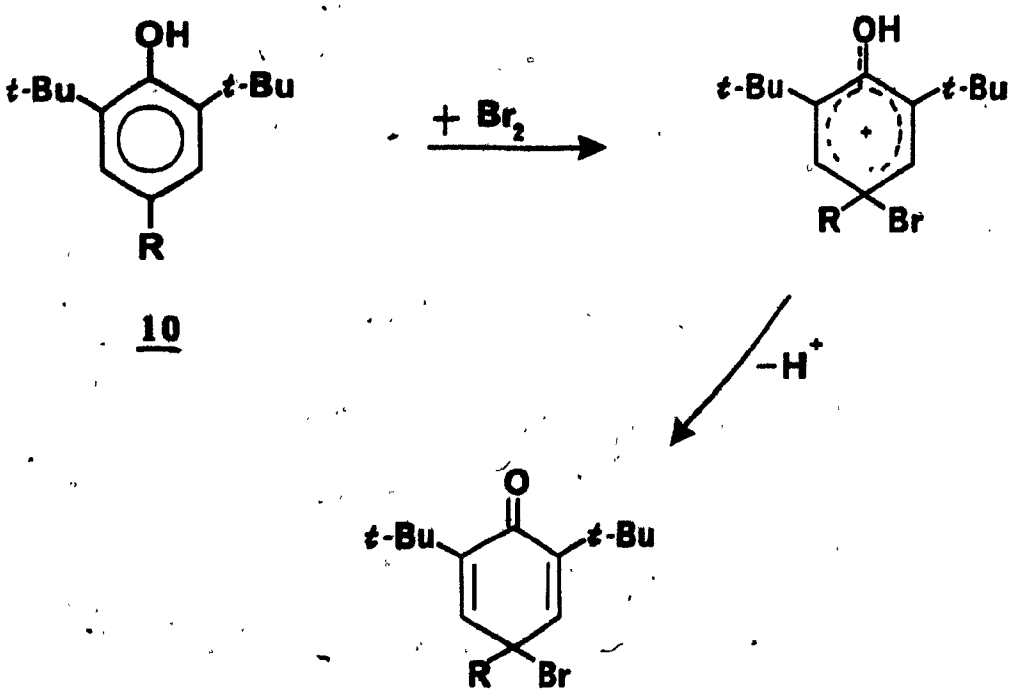
Scheme 1



is presumed to be via the protonated intermediate b. But under normal conditions of bromination the reaction is via the intermediate c. In fact, the build-up and decay of c (absorption at 255 nm) was observed in the presence of acetic acid and sodium acetate. Under these conditions formation of b is not involved but the

pathway suggested is a ⟶ c ⟶ d.[18]

Baciocchi and Illuminati[19] measured the rate of formation of the ipso-dienones of the 4-substituted 2,6-di-t-butylphenol in acetic acid (equation 3). The influence of



10

11

(3)

the nature of the group R on the rate of attack of bromine was studied. The effect of R was anticipated to be either polar or steric. Polar effects seem to effect the rate of reaction considerably since attack on 10 (R = Me) is > 830,000 times that on 10 (R = Br). In terms of steric effects, the reactivity ratio 3.7 relative to 10 (R = H) remains practically unchanged for the substrates 10 (R = Me and t-Bu). Any increase in the steric factor is believed to be balanced by a change in the electron-repelling polar effect of the alkyl group. Overall the order of reactivity for R in the 4-position is given as H > Me $\simeq$ t-Bu and this is justified as being to a combination of polar and steric effects which probably act in opposing directions. In the formation of the dienone the steric effect is probably not large because the bulky R group changes from a coplanar aromatic position to a non-coplanar geminal position. From other aromatic substitution data and the data for dienone formation they propose that the formation of dienone and aromatic substitution proceed via the same type of transition state (benzenonium ion intermediate) for their rate determining steps.[19]

4-Bromo-2,5-cyclohexadienone intermediates also have been detected from the reaction of 2,6-disubstituted

phenols with bromine in acetic acid medium by the use of high-resolution flow NMR by Fyfe.[20,21] For the substrate 2,6-di-t-butylphenol the decomposition of the intermediate was found to be relatively slow and could be monitored by stopping the flow and by rapid, repeated scanning. The decomposition of the intermediate was found to be a first-order process and the half-life was 49 s (in 90 % aqueous acetic acid at 25° C).

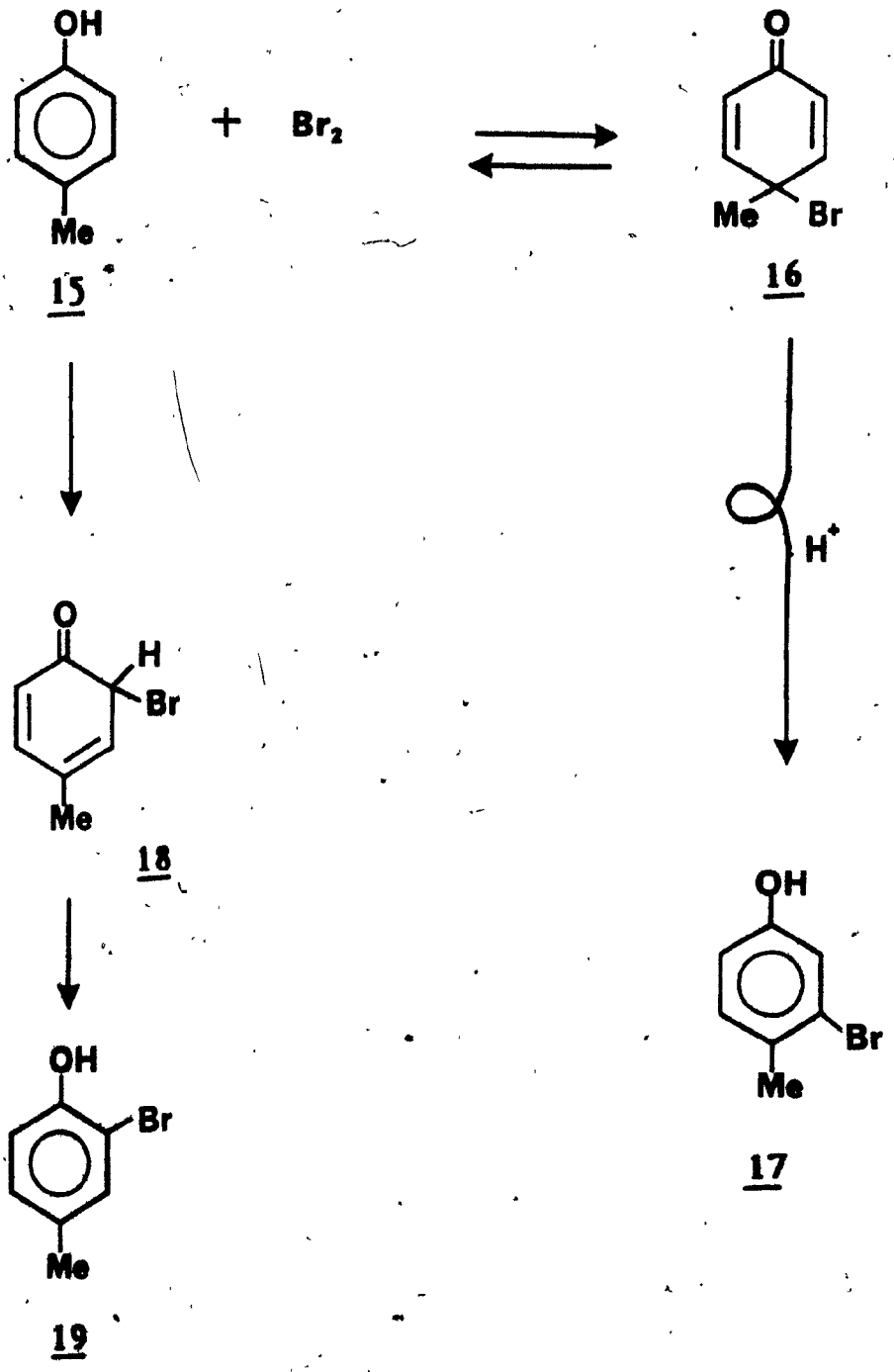
Studies were also done at different temperatures and concentrations of acetic acid to determine the optimum conditions for stabilizing the intermediate. It was observed that at low temperatures and low concentrations of acetic acid (higher concentrations of water) the dienone type of intermediate had longer life time. It was observed that at 15° C and in 85 % acetic acid the half-life of 4-bromo-2,6-di-t-butyl-2,5-cyclohexadienone was 240 s. This confirms the earlier idea of Ershov that solvents which act as proton acceptors stabilize the cyclohexadienones. Experiments carried out with 2,5-di-sec-butylphenol and bromine over a temperature range of 10-30° C and a range of concentrations of acetic acid showed that in all cases the intermediate was very short lived in sharp contrast to the case of the intermediate from 2,6-di-t-butylphenol. Similar results were

observed with 2,6-di-isopropylphenol, 2-t-butyl-6-methylphenol and 2,6-dimethylphenol as substrates.[20] These results reemphasize that the stabilities of the cyclohexadienone intermediates depend very markedly on the steric effects of the groups at 2- and 6-positions of the phenol. For monoalkylphenols and for phenol itself cyclohexadienone intermediates were not detected using the flow NMR technique even under optimal conditions.

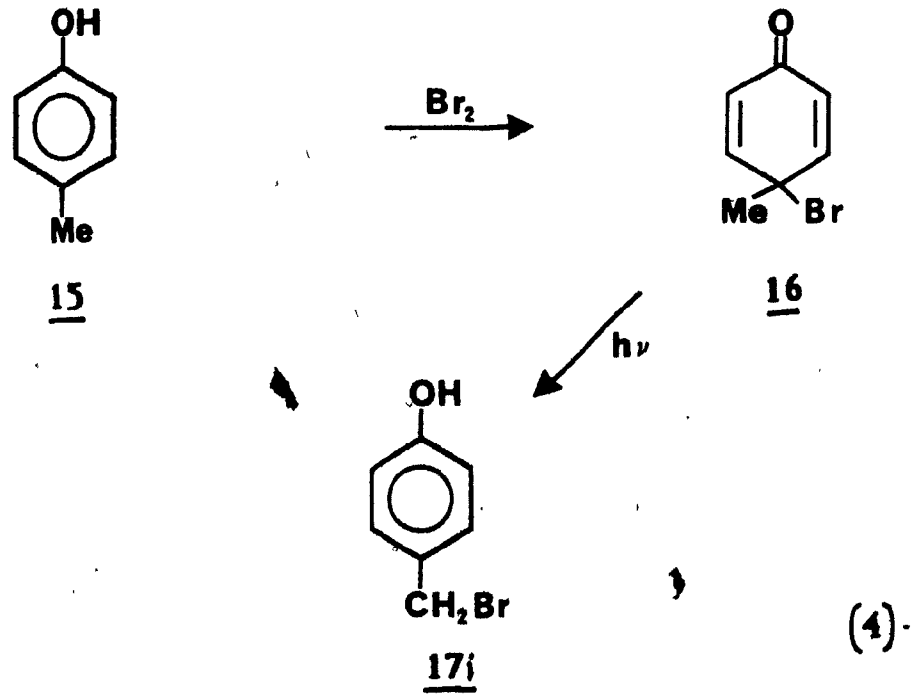
In case of p-alkyl phenols ipso intermediates can be formed along with o-dienones. For example, in bromination of p-cresol (4-methylphenol) (15) (Scheme 2) in acetic anhydride the initial bromination can occur at either 2-position or 4-position (ipso). The former presumably leads to the formation of 2-bromo-4-methyl-3,5-cyclohexadienone (18) and thence to the product 19 and the latter forms 4-bromo-4-methyl-2,5-cyclohexadienone (16) (ipso dienone).[22] The ipso bromination is reversible as the bromide ion can bring about debromination of bromodienone to give p-cresol (15). But in the presence of strong acids (like triflic acid) the bromo substituent migrates to the 3-position giving rise to 3-bromo-4-methylphenol (17).[22]

De la Mare and his co-workers have studied the ipso-dienone formed from the bromination of p-cresol,[24] 2,6-

Scheme 2



dibromo-3,4-dimethylphenol[23], 2,4-dimethylphenol, 4-t-butyl-2-methylphenol[25] and their rearrangements in acids and under powerful illumination.[24] The ipso-dienone in acidic media gave products similar to 17 (Scheme 2) but with light gave product of the type 17i (equation 4).

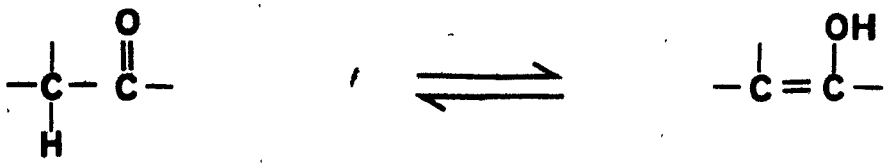


(4)

In the nitration of p-cresols Coombes et al have reported the observation of ipso-dienones and monitored their decay at 230 - 255 nm.[26] With p-substituted anisoles ipso-dienones have also been observed in nitration reactions.[27]

Enolization:

The conversion of the substituted cyclohexadienone to the product is essentially an enolization reaction Enolization is one of the most well-documented processes in Organic Chemistry.[28] It can be illustrated by a simple example (equation 5).

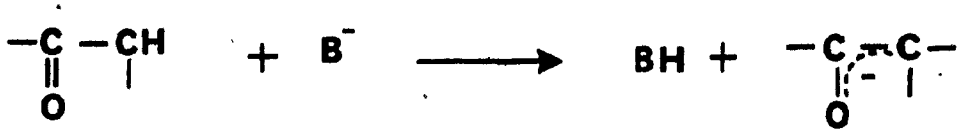


(HS) (SH) (5)

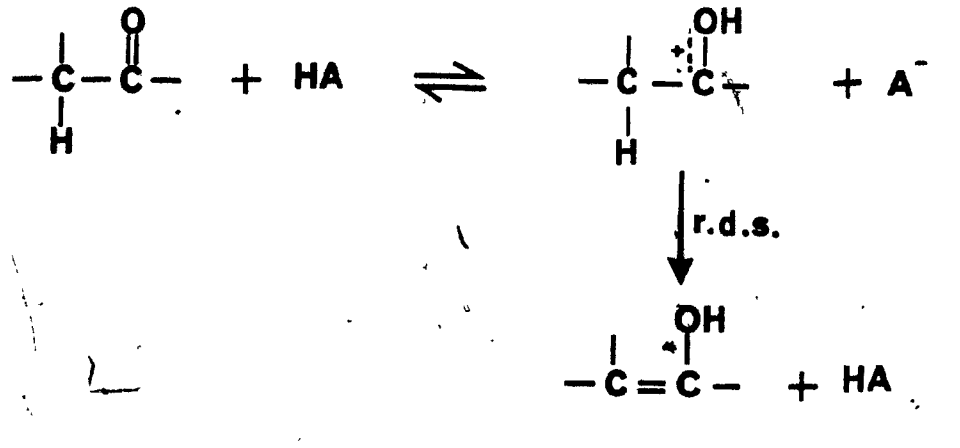
This is also an example of prototropic rearrangements in which there is a proton transfer from a carbon atom to an hetero atom, in this case oxygen. Therefore an insight into enolization can lead to the mechanism of acid-base catalysis. In the case of simple keto-enol tautomeric systems the keto form is more stable than the enol form and the equilibrium is being displaced towards the keto form. Thus in these systems the enol concentration cannot be usually measured as a function of time to study the keto-enol tautomerization. In many reactions of the carbonyl

compounds with electrophilic reagents the reaction occurs via the enol or the enolate form and usually enolization is the rate limiting step. Therefore, for keto-enol tautomerism studies of carbonyl compounds the rate of enolization can be determined from any of several electrophilic reactions.

Enolization reaction can be catalysed by both acids and by bases. Base-catalysed enolate formation can be represented by equation 6 and the specific acid / general base catalysis can be represented by equation 7.



(6)

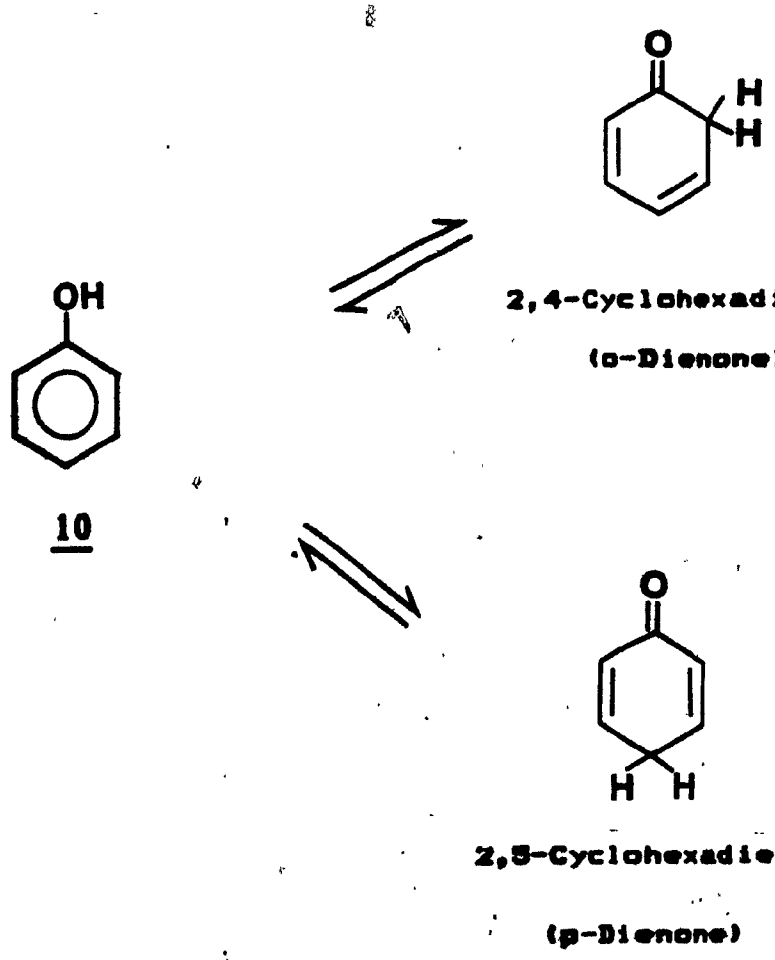


(7)

For the determination of the keto-enol equilibrium constant the rate of ketonization is also essential and for this process the starting material enol is necessary. The mechanism proposed by Toullec[28] for the ketonization of enols is a two-step mechanism, which is simply the reverse of specific acid / general base catalysed enolization (equation 7). Enols do not exist in equilibrium to any great extent with simple aldehydes and ketones but several examples of "kinetically stable" enols in the gas phase or in aprotic solvents have been reported (e.g. enol of acetone in acetonitrile). Free enols have also been generated from photochemical processes (Norrish type II reactions) (e.g. enol of acetophenone)[29] and the rate of ketonization of the generated enols have been studied (e.g. vinyl alcohol ketonization[30] and ketonization of the enol of acetophenone).[31] From these rates of enolization and ketonization the tautomeric equilibrium constant K_E has been calculated for example the pK_E for acetone as determined by kinetic methods is 7.02.[28]

In principle similar studies can be carried out with phenols as phenols also should be able to undergo tautomerization to form cyclohexadienones. Tautomerization in the case of phenols will be more interesting since this

phenomenon is here associated with the breakdown of the aromatic system. Phenols can undergo tautomerization to form cyclohexadienones of two types: (equation 8)



(8)

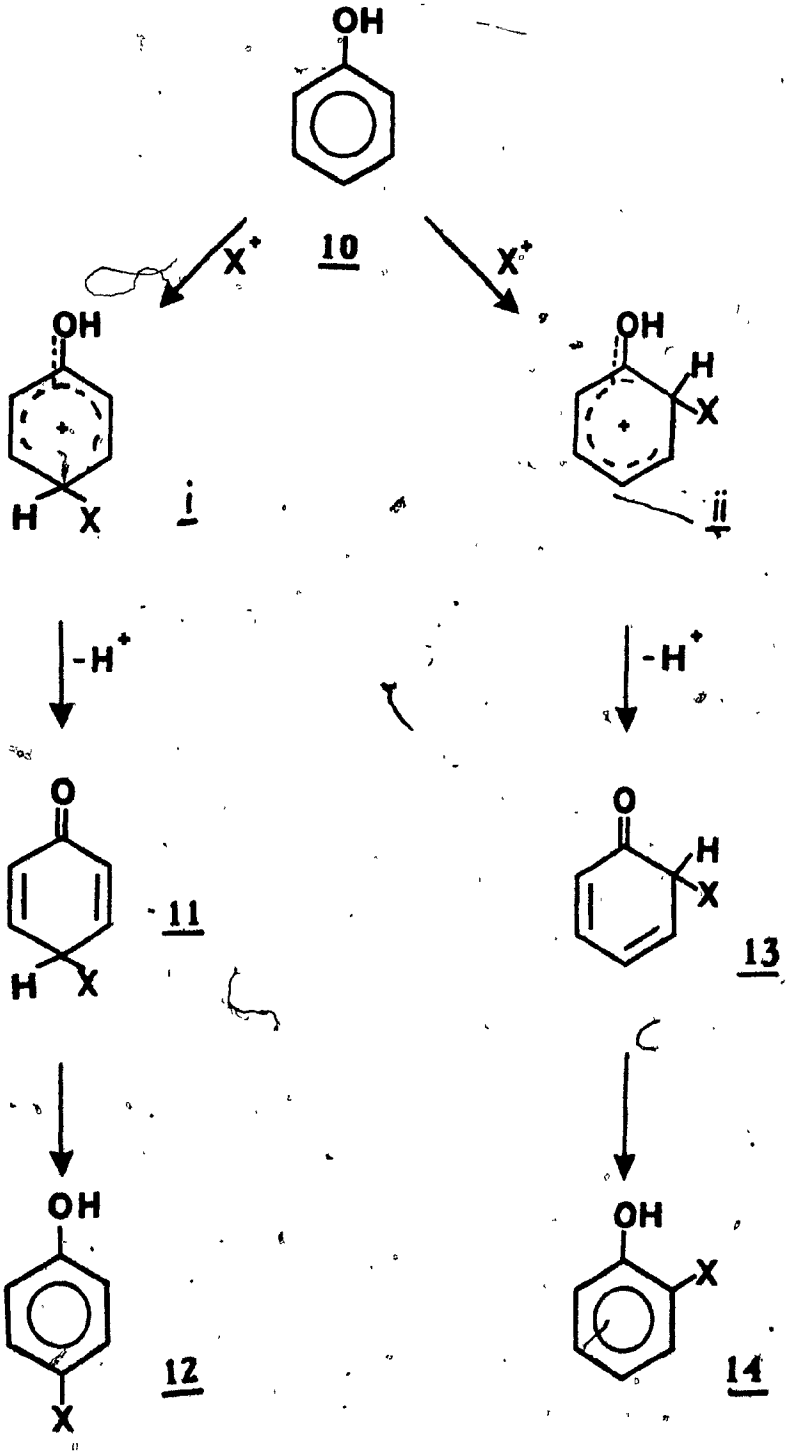
The reaction is essentially the conversion of an aromatic molecule with a hydroxyl to an alicyclic carbonyl compound (o- or p-dienones). In case of phenols, the equilibrium is displaced almost completely towards phenol

(enolic form). Therefore this keto-enol type of tautomerism mechanism has not been studied in phenols. But its mechanism is proposed to be very close to that of electrophilic substitution reactions of phenols.[13] The rate of formation of the cyclohexadienone intermediate should correspond to rate of ketonization and the rate of the decay of the intermediate cyclohexadienone should relate to the rate of enolization. The electrophilic substitution reaction in phenol can be represented as in Scheme 3 and this involves an initial benzenonium type of intermediate formation which, by proton elimination, forms the cyclohexadienone intermediate. If X = H in the Scheme 3 then the mechanism will refer to typical keto-enol tautomerism of phenol itself.

The phenol-dienone type of tautomerism is characterised by the extreme stability of the phenolic (enol) form. The formation of the dienone occurs at the expense of loss of aromaticity, which in terms of energy is about 36 kcal $mole^{-1}$. This is the major reason why simple phenols exist mainly in the enolic form. The possibility of significant tautomerism in simple phenols occurs only when there are additional factors contributing in some way to decrease the differences between the energies of enolization

Scheme 3

Electophilic Substitution in Phenol



and aromatic conjugation.[13] Some of the factors are:

(i) The number of hydroxyl substituents on the aromatic ring. In this case tautomerism may be exhibited as the energy of ketonization of several hydroxyl groups may be greater than the resonance energy of an aromatic ring.

(ii) Formation of phenoxide ion. The negative charge is redistributed due to resonance in the phenoxide ion which may facilitate the formation of the dienone.

In the tautomerism of 2,6-disubstituted phenols steric factors result in greater stability of the keto forms and retard their rearrangement to the phenol.[13]

Buffer Catalysis:

Reactions which show increase in rate with increase in buffer concentrations at constant pH and ionic strength are designated as buffer-catalysed reactions. A plot of the slopes of buffer plots versus the fraction of free base will indicate which component of the buffer is catalysing the reaction. The intercepts from such plots are associated with the catalytic constants k_A and k_{HA} for the basic and acidic components of the buffer, respectively.

With increase in base strength of the catalyst, the catalytic constant k_A or the efficiency of the general

base catalysis increases. A plot of log k_A against pK_a gives a slope generally designated as Bronsted exponent β . The parameter β is a measure of the sensitivity of the reaction to the strength of the basic catalyst. This relationship can be represented by Bronsted equation as in 9:

$$\log k_A = \log G_B + \beta (pK_a) \qquad (9)$$

where G_B is a reaction constant. For the enolization of acetone the reported value of β is 0.88.[28]

The Bronsted exponent α is a measure of the sensitivity of a reaction to the acid strength of general acid catalysts. It is the slope obtained from the plot of catalytic constant k_{HA} against pK_a of the acid. This Bronsted relationship is given as in equation 10:

$$\log k_{HA} = \log G_A - \alpha (pK_a) \qquad (10)$$

where G_A is the reaction constant.

The α value for the enolization of acetone is 0.55 which is explained by specific acid catalysis and a value of β for the general base catalysis $(1-\alpha)$ is 0.45.[28] Values of α and β provide a measure of the degree of proton transfer in a rate-limiting transition state.[28]

Salicylic Acid:

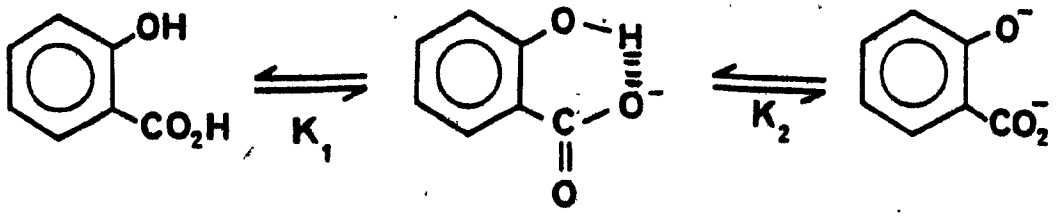
It has been established that salicylic acid (5) is a stronger acid compared to the m- or p-hydroxybenzoic acid (Table I). This behaviour is ascribed to an intramolecular hydrogen-bond which stabilizes the salicylate monoanion to a greater extent than it does the unionized acid.[36]

Table I

pK_a's of Hydroxybenzoic Acids

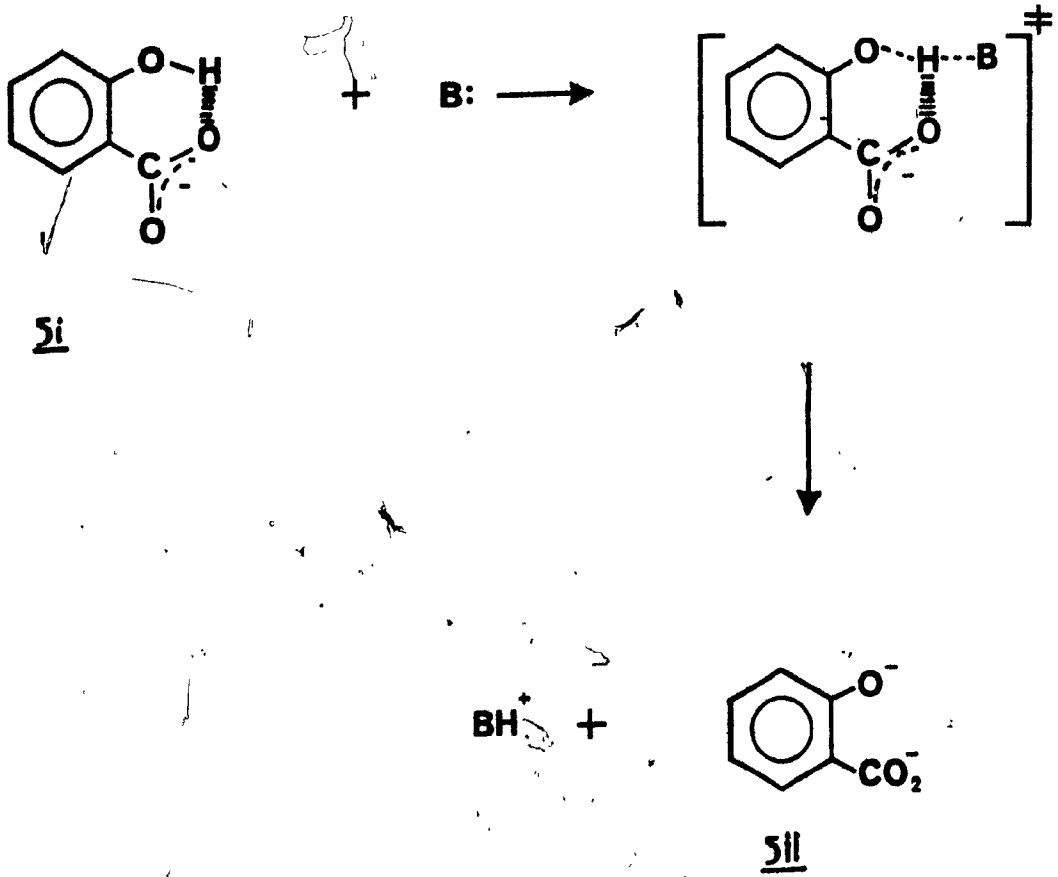
Compound	pK_1	pK_2
Salicylic acid	2.98	13.61[51]
m-Hydroxybenzoic acid	3.90	9.78[46]
p-Hydroxybenzoic acid	4.61	9.31[46]

The ionisation of salicylic acid (5) can be shown as follows (equation ii)



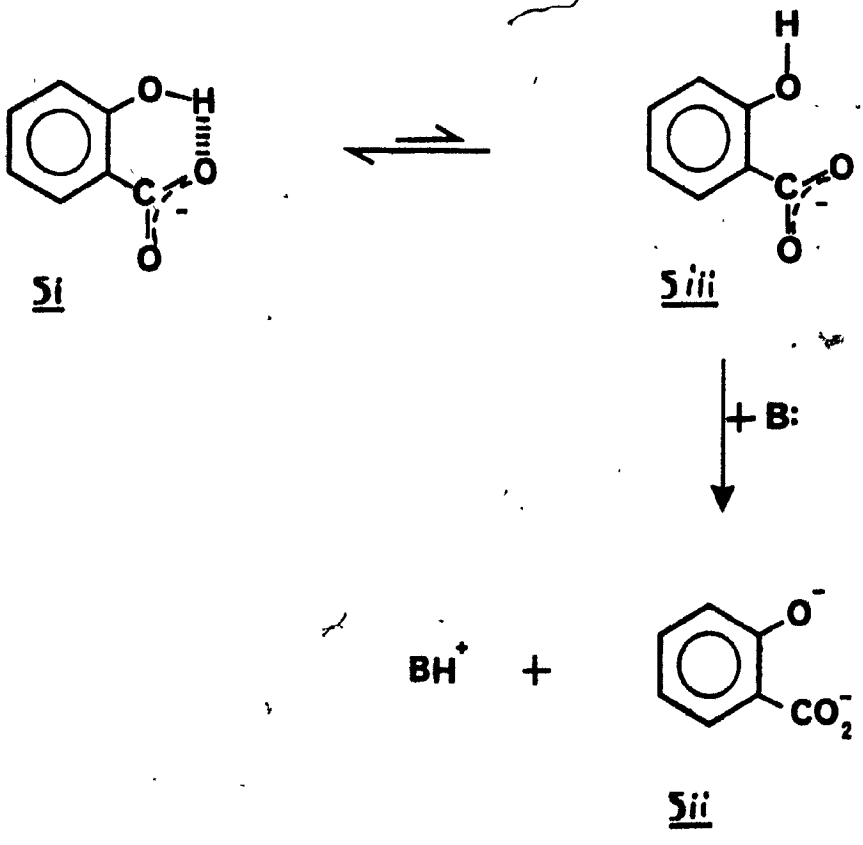
5 5i 5ii (ii)

The mechanism of proton transfer from intramolecularly hydrogen bonded acids has been studied by Hibbert.[33] Two mechanisms have been suggested for the transfer of proton from the salicylate monoanion to bases. One is via the concerted pathway which involves the cleavage of the intramolecular hydrogen-bond and proton transfer to the base:



5i 5ii (12)

Another mechanism is the two-step process involving a rapid equilibrium between hydrogen-bonded (5i) and non-hydrogen-bonded (5iii) forms of the salicylate anion with proton transfer occurring from the non-hydrogen-bonded (5iii) form which is present in low concentration (equation 13).



(13)

Apparently the second mechanism is thermodynamically preferred as kinetic data are consistent with this two-step process.[33]

Prior to the present work the aqueous bromination of salicylic acid has been studied by Rao and Mali.[34] They used a continuous-flow system and electrochemical method to measure the concentration of bromine during the course of reaction. The second-order rate constant at 25° C reported by them was 4.2×10^{5} M^{-1} s^{-1} for unbuffered media.[34] It is not easily compared to our results obtained at fixed pH.

Objectives:

The work carried out for this thesis can be grouped broadly into five sections.

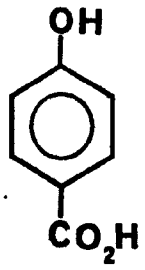
1. The main project was to study the bromination of salicylic acid and its derivatives and observe the effect, if any, of the intramolecular hydrogen-bond on the ease and mechanism of the reaction. This work has been submitted for publication.
2. As a control for the above study the bromination of p- hydroxybenzoic acid and its derivatives was also studied. It was found that this control system behaved abnormally and the results of this study have recently been published.[39]
3. The formation and decay of 4-bromo-2,5-cyclohexadienone intermediate at 240-245 nm was noticed while determining the rate of bromination of phenol in 0.1 M KBr. This has led to various studies dealing with cyclohexadienones. In particular, their enolization to form the product and the importance of general acid-base catalysis on the enolization reaction was studied in detail. Following an initial communication,[37] the bulk of this study has been published recently.[38]

4. The interest in the dienone type of intermediates was extended to the study of ipso-dienone type of intermediates which can be formed from 4-substituted phenols. The study was concerned with the type of catalysis in the debromination of these ipso-dienones and it was found that the reaction is general acid-catalyzed.

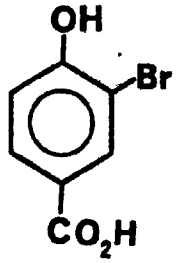
5. If the debromination of dienone is general acid-catalyzed then the formation of the dienone must be general base-catalyzed. Some buffer catalysis studies were carried out to show that the attack of bromine on phenol is general base-catalyzed, providing additional support to Paventi's work.[10] Overall in the bromination of phenol it appears that the formation of dienone is general base-catalyzed and that the enolization of the dienone is general acid-catalyzed.

Bromination of p-Hydroxybenzoic Acid and some Derivatives.

The bromination of p-hydroxybenzoic acid (1) and some of its derivatives was studied as a "control system" for the study of salicylic acid (5) and its derivatives. The rates of reaction of bromine with p- hydroxybenzoic acid (1), 3-bromo-4-hydroxybenzoic acid (2), p-anisic, acid (3) and ethyl 4-hydroxybenzoate (4) have been measured in the pH range of 0-6. These reactions are fast, requiring the use of the stopped-flow technique to successfully monitor the progress of the reaction.



1



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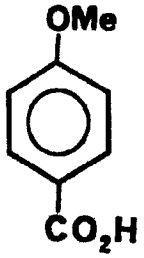

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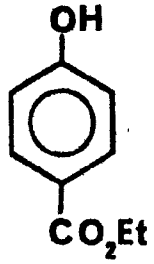


4

In the presence of at least a ten-fold excess of substrate good first-order rate constants (k_1^{obsd}) were obtained for the rate of disappearance of bromine. The values of k_1^{obsd} were found to be a direct function of the substrate concentration indicating a overall second-order behaviour at fixed pH, i.e. the reaction is first-order in substrate and bromine. The values of k_1^{obsd}, were converted to second-order rate constants k_2^{obsd}, taking into account the substrate concentration and correcting for the reduction in free molecular bromine due to the formation of tribromide ion and, where necessary, hypobromous acid.[40]

Results:

The pH-dependences of the second-order rate constants of the four substrates 1-4 were determined in aqueous acids and in buffers. The results are shown in Table II and in the pH - rate profile in Figure 1. The shapes of these rate profiles are as expected for the various forms.

The rate profile for the ethyl 4-hydroxy-benzoate (4) is similar to the profiles of other simple p-substituted phenols.[9-11] Below pH 2 the rate is independent of pH representing the attack of bromine on 4 itself, followed by a region where the rate increases with pH corresponding to the

Table II

Rate Constants for the Reaction of Bromine with p-Hydroxybenzoic Acid (1), 3-Bromo-4-hydroxybenzoic Acid (2), p-Anisic Acid (3), and Ethyl 4-hydroxybenzoate (4).[a]

Substrate	pH	k_2^{obsd} ($M^{-1}s^{-1}$)
(1)[b]	0.11	3.04×10^{3} •
	0.43	3.71×10^{3} •
	0.86	3.62×10^{3} •
	1.00	4.24×10^{3}
	1.40	4.69×10^{3}
	1.68	6.24×10^{3}
	2.00	8.78×10^{3}
	2.41	1.18×10^{4}
	2.61	2.13×10^{4}
	3.11	5.03×10^{4}
	3.41	1.01×10^{5}
	3.95	4.42×10^{5}
	4.35	7.43×10^{5}
	4.84	1.44×10^{6}
	5.22	2.20×10^{6}

Table II (Cont'd)

Substrate	pH	k_2^{obsd} ($M^{-1}s^{-1}$)
	5.94	4.13×10^{6}
	6.07	5.26×10^{6}
(2)	0.00	7.27×10^{2} [b]
	0.50	3.03×10^{3} [c]
	1.00	6.26×10^{3} [b]
	1.50	1.79×10^{4} [c]
	2.12	5.73×10^{4} [b]
	2.45	1.45×10^{5} [c]
	3.11	5.14×10^{5} [b]
	3.42	1.20×10^{6} [c]
	4.16	3.34×10^{6} [c]
	4.52	4.79×10^{6} [c]
	4.95	4.98×10^{6} [c]
(3)[c]	3.24	22.7
	4.08	95.4
	4.46	172
	5.04	234
	5.53	235
	6.33	244

Table II (Cont'd)

Substrate	pH	k_2^{obsd} ($M^{-1}s^{-1}$)
(4)[c]	0.00	1.71×10^{3}
	0.52	2.14×10^{3}
	1.00	2.91×10^{3}
	1.52	3.95×10^{3}
	2.00	6.47×10^{3}
	2.99	2.89×10^{4}
	4.01	2.83×10^{5}
	4.83	2.67×10^{6} [d]

[a] At 25 °C, in 0.1 M KBr, k_2^{obsd} is corrected for tribromide ion and hypobromous acid formation.

[b] (Substrate) = 10^{-4} M and (Bromine) = 10^{-5} M.

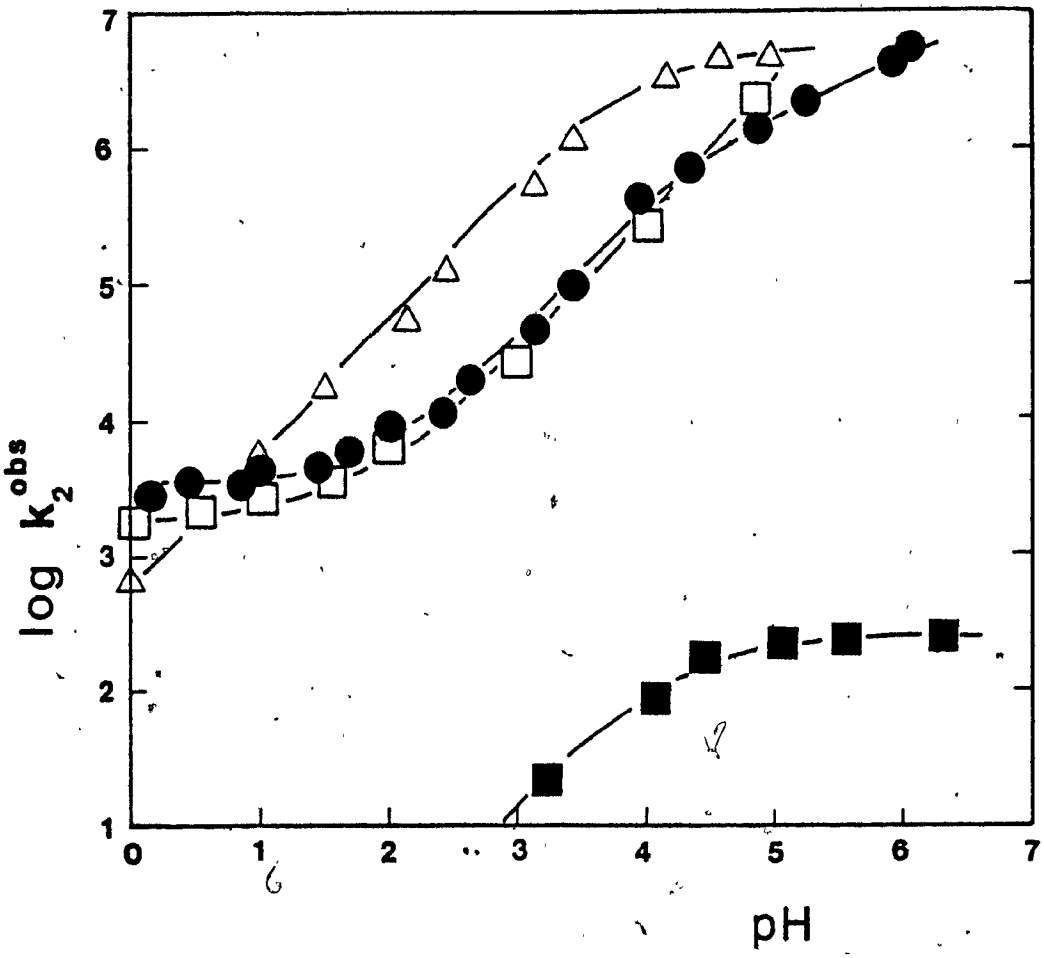
[c] (Substrate) = 5×10^{-4} M and (Bromine) = 5×10^{-5} M.

[d] (Substrate) = 2×10^{-4} M and (Bromine) = 2×10^{-5} M.

[e] Preliminary data obtained by B. Kraus.

Figure 1

Rate-profiles for the bromination of p-hydroxybenzoic acid and its derivatives.



((●) p-hydroxybenzoic acid, (△) 3-bromo-4-hydroxybenzoic acid, (□) ethyl 4-hydroxybenzoate and (■) p-anisic acid.

attack of bromine upon the anion of 4. Overall the data for 4 may be represented by the following equation:

$$k_2^{obsd} = k_2 + k_2'' K_2 / (H^+) \qquad (14)$$

Here k_2 is the rate constant for the attack of bromine on the undissociated form of 4, k_2'' for the attack upon the anion of 4 and K_2 is the ionization constant of the phenolic -OH of 4. As will be discussed later, the values of k_2 and k_2'' are comparable to the values observed for other phenols and phenoxides.[9-11]

In the case of p-anisic acid (3) the reactions were quite slow and studies were carried out in a more limited pH-range. In this pH-range it appears that 3 reacts solely as its anionic form, and the rate constant can be given as :

$$k_2^{obsd} = k_2' K_1 / (K_1 + (H^+)) \qquad (15)$$

where k_2' represents the rate constant for the attack of bromine on the anion of 3 and K_1 the dissociation constant of the carboxyl group of 3.

Similarly the rate for the 3-bromo-4-hydroxybenzoic acid (2) can be represented by equation (15). Equation (15) was fitted to the data of 3 and 2 and the

CHAPTER 2

values of k_2' and K_1 (expressed as pK_1) obtained for these substrates are given in Table III.

The rate profile for the p-hydroxybenzoic acid (1) does not seem to be as simple as the rate profiles discussed above. At pH < 1.5 the rate is invariant of pH suggesting the attack of bromine upon the undissociated form of 1. In the pH range of 2-4 the rate profile is consistent with reaction upon the monoanion of 1 (1a). But above pH 4.7 ($>pK_1$) the data does not show a distinct plateau as expected. The increase in rate at higher pH may be due to the onset of the reaction of bromine with the dianion of 1 (1b). The ionization of 1 to its anions is represented in Scheme 4. To accomodate the reaction upon the dianion, Equation (15) is modified and the expected form of k_2^{obsd} for 1 is given by Equation 16.

$$k_2^{obsd} = \frac{k_2(H^+) + k_2' K_1}{(K_1 + (H^+))} + \frac{k_2'' K_2}{(H^+)} \qquad (16)$$

Where k_2, k_2' and k_2'' are the rate constants for the attack of bromine upon the undissociated form 1, monoanion (1a) and dianion (1b) respectively, K_1 and K_2 are the first and second acid dissociation constants of 1. Values of k_2, k_2' and k_2'' and K_1 were obtained by fitting Equation

(16) to the data , the literature value of K_2 being assumed. These values are in Table III together with the values for the other substrates. The various constants in Table III which were obtained from fitting to the kinetic data all are much as expected except for the values of k_2' for the mono-anions of 1 and 2. As will be discussed below, these constants appear to be 9 times and 5200 times greater than anticipated.

Discussion:

From the rate profiles (Figure 1) it is significant that the profile for p-anisic acid (3) is much below that for p-hydroxybenzoic acid (1). This suggests a much greater reactivity (10,000 times) of the p-hydroxybenzoate anion (1a) than that of the p-anisate anion (refer to Table III) for the reaction with bromine. This high reactivity ratio seems to be unusual when compared to the other phenol / anisole ratios. The second-order rate constants for phenol[10] and anisole[41] are 4.2×10^5 M^{-1} s^{-1} and 3.6×10^4 M^{-1} s^{-1} (ratio :12) and that of p-bromophenol[42] and p-bromoanisole[41] are 3900 M^{-1} s^{-1} and 3.3 $M^{-1}s^{-1}$ respectively (ratio : 1200).

Table III

Comparison of the Kinetic Parameters for the Bromination of p-Hydroxybenzoic acid (1), 3-Bromo-4-hydroxybenzoic acid (2), p-Anisic acid (3) and Ethyl 4-hydroxybenzoate (4).[a]

Compound	k_2	k_2'	k_2''	pK_1	pK_2
1	3500	2.6×10^6	3.5×10^5	4.80 (4.61)[46]	(9.31)[46]
2		5.6×10^6		3.97 (4.03)[b]	
3		260		4.26 (4,52)[46]	
4	2200		8.2×10^9		(8.50)[32]

[a] At 25 °C, ionic strength = 0.11 M. Values of pK's in parentheses are measured values; those without parentheses are from fitting. Units of k_2's are $M^{-1}s^{-1}$.

[b] Measured spectrophotometrically.

The next significant feature to note from Figure 1 is that the profile for 3-bromo-4-hydroxybenzoic acid (2) lies above that of the parent, 1. This implies that the monoanion 1a is less reactive than the monoanion of 2 for the bromination reaction , contrary to the expected deactivating effect of a meta-bromo substituent on electrophilic attack (σ^{+}_{m} = 0.405).[43]

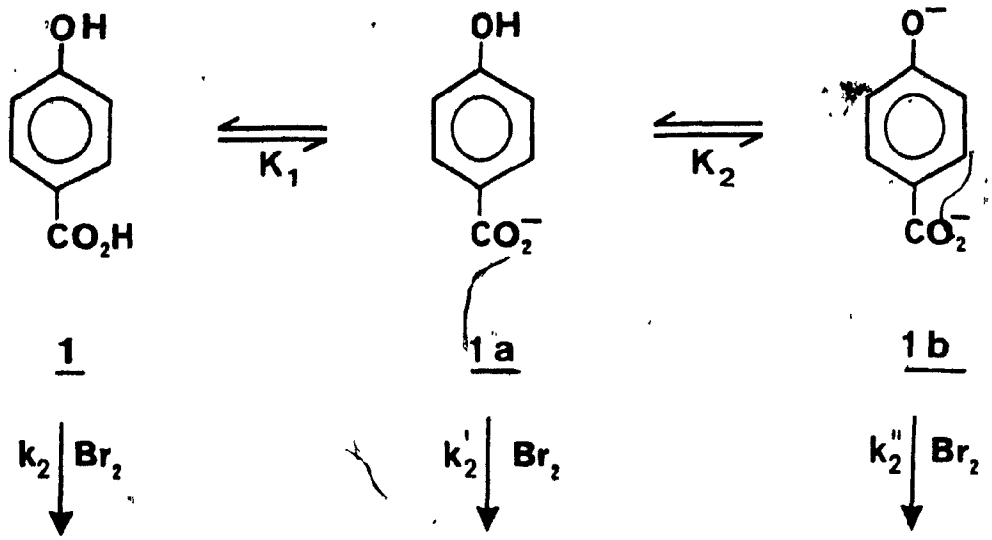
The third point of interest to note from Figure 1 is that the profile for ethyl 4-hydroxybenzoate (4) lies almost exactly on that of p-hydroxybenzoic acid (1). At pH < 2 both these substrates react with bromine via their undissociated form and such correspondence is reasonable since the substituent effects of $-CO_2H$ and $-CO_2Et$ are very similar. Between pH 2 - 4 both the rate profiles are quite similar and, as this is the region where 4 reacts via its anion (4- carboethoxy phenoxide) it is likely that the anion 1a reacts via its tautomer, 4-carboxy phenoxide, 1c. The detailed mechanisms will be discussed later in this section.

For Scheme 4 the rate of bromination of p-hydroxybenzoic acid (1) is given by

$$\text{rate} = (k_2 (1) + k_2' (1a) + k_2'' (1b)) (Br_2) \qquad (17)$$

The observed data require $\text{rate} = k_2^{obsd} (1)_T (Br_2)$ (18)

Scheme 4



$$\text{or } k_2^{obsd} = \frac{(k_2 (\underline{1}) + k_2' (\underline{1a}) + k_2'' (\underline{1b}))}{(\underline{1})_T} \quad (19)$$

where $(\underline{1})_T = (\underline{1}) + (\underline{1a}) + (\underline{1b})$ (20)

$(\underline{1b})$ is negligible at pH below 6 as pH $\ll$ pK_2 (= 9.31).[46]

$$\therefore (\underline{1})_T = (\underline{1}) + (\underline{1a}) \quad (21)$$

$$K_1 = \frac{(\underline{1a})(H^+)}{(\underline{1})} = 10^{-4.61} \quad \text{for } \underline{1}.[46] \quad (22)$$

$$K_2 = \frac{(\underline{1b})(H^+)}{(\underline{1a})} = 10^{-9.31} \quad \text{for } \underline{1a}.[46] \quad (23)$$

From equations 21 and 22

$$\frac{(1a)}{(1)_T} = \frac{K_1}{K_1 + (H^+)} \qquad (24)$$

and from equations 23 and 24

$$\frac{(1b)}{(1)_T} = \frac{K_1 K_2}{(H^+)(K_1 + (H^+))} \qquad (25)$$

Equation 19 can be rewritten as

$$k_2^{obsd} = \frac{k_2(H^+) + k_2' K_1}{(K_1 + (H^+))} + \frac{k_2'' K_1 K_2}{(H^+)(K_1 + (H^+))} \qquad (26)$$

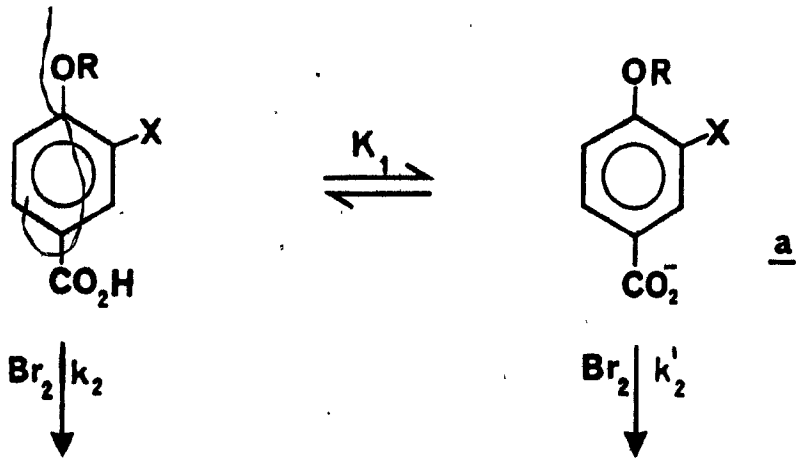
At pH's where the last term is significant pH > pK_1 and so equation 26 can be reduced to :

$$k_2^{obsd} = \frac{k_2(H^+) + k_2' K_1}{(K_1 + (H^+))} + \frac{k_2'' K_2}{(H^+)} \qquad (27)$$

Equation 27 is same as equation 16 which was used to fit to the data of 1. Thus the observed data are consistent with reaction taking place upon the neutral species at higher acidity, upon the monoanion around pH 2-4 and the plateau region being very small due to reaction upon the dianion at pH >5.

The situation for p-anisic acid (3) and 3-bromo-4-hydroxybenzoic acid (2) can be represented as in Scheme 5.

Scheme 5



	2	3
R	H	Me
X	Br	H

From the Scheme 5 the rate of reaction for 3-bromo-4-hydroxybenzoic acid (2) can be represented as

$$\text{rate} = (k_2 \{ \underline{2} \} + k_2' \{ \underline{2a} \}) \{ Br_2 \} \quad (28)$$

whereas the observed rate $= k_2^{obsd} \{ \underline{2} \}_T \{ Br_2 \}$ (29)

$$\text{Therefore} \quad k_2^{obsd} = \frac{k_2 \{ \underline{2} \} + k_2' \{ \underline{2a} \}}{\{ \underline{2} \}_T} \quad (30)$$

$$\text{But} \quad \{ \underline{2} \}_T = \{ \underline{2} \} + \{ \underline{2a} \} \quad (31)$$

and $$K_1 = \frac{(\underline{2a})\ (H^+)}{(\underline{2})} \qquad (32)$$

Combination of eqations 30, 31 and 32 and rearrangement gives

$$k_2^{obsd} = \frac{k_2\ (H^+) + k_2'\ K_1}{K_1 + (H^+)} \qquad (33)$$

For 3-bromo-4-hydroxybenzoic acid (2) the rate profile does not level off even at lower pH's indicating that even at pH 0 the reaction is mainly via its anion 2a. In case of p-anisic acid (3) in the pH range studied the attack of bromine is mainly on the monoanionic form (3a). Therefore the first term $k_2\ (H^+) / K_1 + (H^+)$ in equation 33 can be eliminated and equation 33 can be reduced to

$$k_2^{obsd} = \frac{k_2'\ K_1}{K_1 + (H^+)} \qquad (34)$$

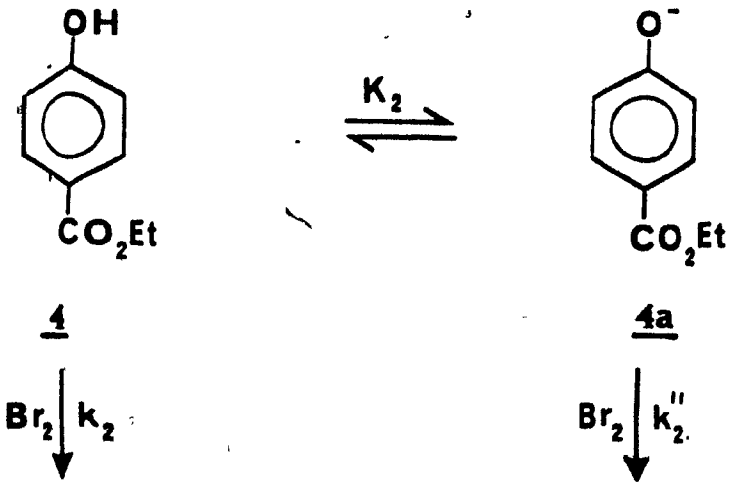
Equation 34 is the same as equation 15 which was used to generate the calculated curve in Figure 1 for substrates 2 and 3.

The bromination of ethyl 4-hydroxybenzoate (4) can be represented as in Scheme 6.

$$rate = (k_2\ (\underline{4}) + k_2''\ (\underline{4a})) \qquad (35)$$

$$\text{Observed rate} = k_2^{obsd} \, (\underline{4})_T \, (Br_2) \qquad (36)$$

Scheme 6



Combining equations 35 and 36

$$k_2^{obsd} = \frac{k_2 \, (\underline{4}) + k_2'' \, (\underline{4a})}{(\underline{4})_T} \qquad (37)$$

$$(\underline{4})_T = (\underline{4}) + (\underline{4a}) \qquad (38)$$

$$K_2 = \frac{(\underline{4a}) \, (H^+)}{(\underline{4})} \qquad (39)$$

Combination of equations 37, 38 and 39 and rearrangement gives

$$k_2^{obsd} = \frac{k_2 \, (H^+) + k_2'' \, K_2}{K_2 + (H^+)} \qquad (40)$$

At the pH's used in this study $(H^+) >> K_2$ and so equation 40 reduces to

$$k_2^{obsd} = k_2 + \frac{k_2'' K_2}{(H^+)} \qquad (41)$$

Equation 41 is the same as equation 14 used to fit the kinetic data for substrate (4) indicating that in the pH invariant region the attack of bromine is upon the neutral species 4 and at higher pH the reaction is via its anion 4a.

Before a detailed mechanism for these substrates bromination is discussed a brief description about the apparent reactivities of the substrates and their reactive forms will be considered. Ethyl 4-hydroxybenzoate (4), behaves like a typical phenol. Table IV lists the second-order rate constants for the bromination of different p-substituted phenols. The logarithmic values of these rate constants when plotted against σ_m^+ constants give a reasonable Hammett plot (Figure 2 and Table IV). The point for x = CO_2^- does not seem to fit into the line along with the other points and excluding this point of CO_2^- the correlation for the line is r = 0.980.

Table IV

Second Order Rate Constants for the attack of Bromine on p-x-Substituted Phenols.[a]

x	σ_m^+	k_2 ($M^{-1} s^{-1}$)	Ref/ note
Me	-.066	6.2×10^5	42
t-Bu	-.059	5.9×10^5	42
CO_2^-	-.028	2.6×10^6	b
H	0.000	7.6×10^4	c
CO_2H	0.322	3.5×10^3	b
CO_2Et	0.366	2.2×10^3	b
Br	0.405	3.9×10^3	42
CN	0.562	155	42

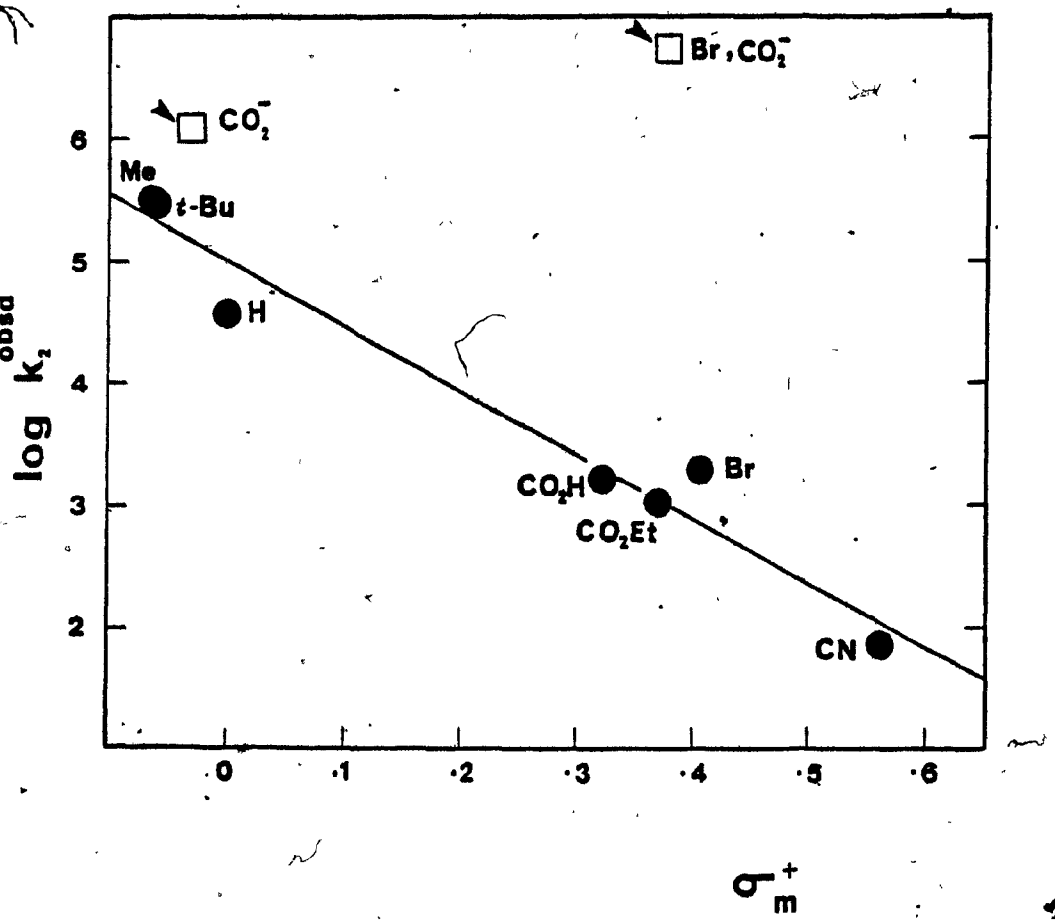
[a] At 25 °C, I= 0.11 M (KBr + buffer). Values of k_2 corrected for Br_3^- formation. σ_m^+ from ref. 43.

[b] This work.

[c] Based on $k = 4.2 \times 10^5$ M^{-1} s^{-1} for phenol and the o/p ratio of 18/82 (ref. 10).

Figure 2

Hammett plot for the bromination of p-substituted phenols.



(intercept = 5.30 (± 0.15), slope = 5.21 (± 0.47) and r = 0.980 (excluding the $-CO_2^-$ point and Br, CO_2^- point)).

$$\log k_2 = 5.30 - 5.21 \sigma_m^+ \qquad (42)$$

If the correlation line is based on all points the value of ρ is -5.68 and r = 0.962. The rate constants for p-hydroxybenzoic acid (1) (x = CO_2H) and its ester 4 (x = CO_2Et) correlate very well with the other rate constants of p-substituted phenols. But the point for the anion 1a (x = CO_2^-) is much above the correlation line. The calculated rate constant k_2' for 1a from equation 42 is 2.8×10^5 M^{-1} s^{-1} (for two ortho positions which is 9.3 times lower than the observed k_2' for 1a (Table III)).

For the 3-bromo-4-hydroxybenzoate anion 2a the deviation is very high. To show the unusual high reactivity of 2a, it is assumed that this rate constant should lie on the line expressed by equation 43.

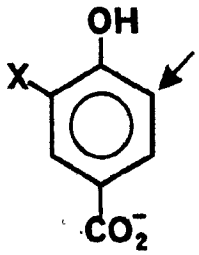
$$\log k_2 = 5.00 - 5.21 \Sigma \sigma_m^+ \qquad (43)$$

(The intercept is reduced by 0.30 compared to equation 42 because there is only one ortho position available in the anion 2a). From equation 43 the calculated rate constant k_2' for 2a is 1086 $M^{-1}s^{-1}$. Compared to this the observed rate constant for 2a is 5200 times greater (see Table V).

The observed rate constant for the anion of ethyl p-hydroxybenzoate (4a), is 8.2×10^9 M^{-1} s^{-1}. This

Table V

Estimated and Observed Rate Constants for the Attack of Bromine on p-Hydroxybenzoate Anions.[a]



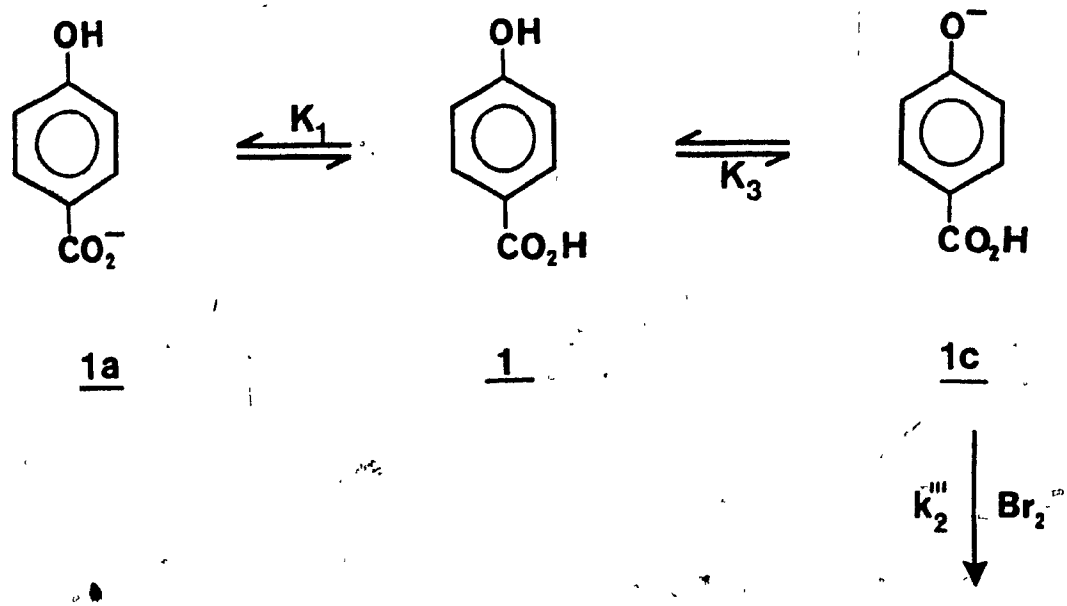
	k_2' ($M^{-1}s^{-1}$)	
	X = H	X = Br
Observed	1.3×10^6	5.6×10^6
Estimated	1.4×10^5	1086
Ratio	9.3	5200

a. Rate constants for X=H have been statistically corrected to correspond to one ortho position

is in agreement with the rate constants observed for other simple phenoxides[9-11,42] which are at the diffusion-controlled limit. The observed rate constant of 3.5×10^9 M^{-1} s^{-1} for the dianion of 1 also falls into this category.

We believe that the apparently abnormal reactivities of the anions 1a and 2a can be explained by the mechanism outlined in Scheme 7.

Scheme 7



The essential feature of this mechanism is that the reaction is via the minor tautomeric form 1c. For Scheme 7 the rate can be represented as

$$\text{rate} = k_2''' \text{ (1c) } (Br_2) \qquad (44)$$

But the observed rate $= k_2^{obsd}\ (\underline{1})_T\ (Br_2)$ (18)

and so

$$k_2^{obsd} = k_2'''\ (\underline{1c}) / (\underline{1})_T \quad (45)$$

where

$$(\underline{1})_T = (\underline{1}) + (\underline{1a}) + (\underline{1c}) \quad (46)$$

(assuming $(\underline{1b})$, the concentration of the dianion to be negligible at pH < 6)

$$K_3 = \frac{(\underline{1c})\ (H^+)}{(\underline{1})} \quad (47)$$

Combining equation 22, 46 and 47 and rearranging gives

$$\frac{(\underline{1c})}{(\underline{1})_T} = \frac{K_3}{(H^+) + K_1 + K_3} \quad (48)$$

From equations 45 and 48 k_2^{obsd} can be written as

$$k_2^{obsd} = \frac{k_2'''\ K_3}{(H^+) + K_1 + K_3} \quad (49)$$

However, as will be apparent shortly, $K_3 << K_1$ and so

$$k_2^{obsd} = \frac{k_2'''\ K_3}{(H^+) + K_1} \quad (50)$$

Equation 50 is algebraically equivalent to equation 34 which is appropriate for the reaction via the major anion $\underline{1a}$. Thus the reaction of the two tautomeric anions $\underline{1a}$ and $\underline{1c}$ are

kinetically indistinguishable. In the region of the rate profile where the reaction via the undissociated form 1 or via the dianion form 1b is negligible the data can be equally represented using equation 50 or 34. In other words the product of $k_2' K_1 = 41.2\ s^{-1}$ obtained by fitting equation 27 to the data for 1 can be equated to $k_2''' K_3$. A value of K_3 can be obtained by using the Hammett correlation for phenols.[45]

$$pK_a = 9.92 - 2.23\ \sigma^-_p \qquad (51)^{45}$$

Using $\sigma^- = 0.728$ for para carboxy substituent[43] the estimated pK_3 for 1 is 8.30. This value seems to be reasonable when compared to the similar pK^- value of the ethyl ester 4 which is 8.50 (Table III). From this K_3 value of $10^{-8.3}$ M the estimated value of k_2''' is $8.2 \times 10^9\ M^{-1}\ s^{-1}$. This value justifies the mechanism in Scheme 7 because the rate constant is the same as that for the anion of ethyl ester 4 (k_2'' Table III).

The reasoning for the anomalous reactivity of 3-bromo-4-hydroxybenzoic acid 2 monoanion can be carried out in a similar fashion. For the major anion of 2 the product $k_2' K_1$ is $600\ s^{-1}$, obtained by fitting equation 34 to the data for 2. This is equated to the term $k_2''' K_3$. The

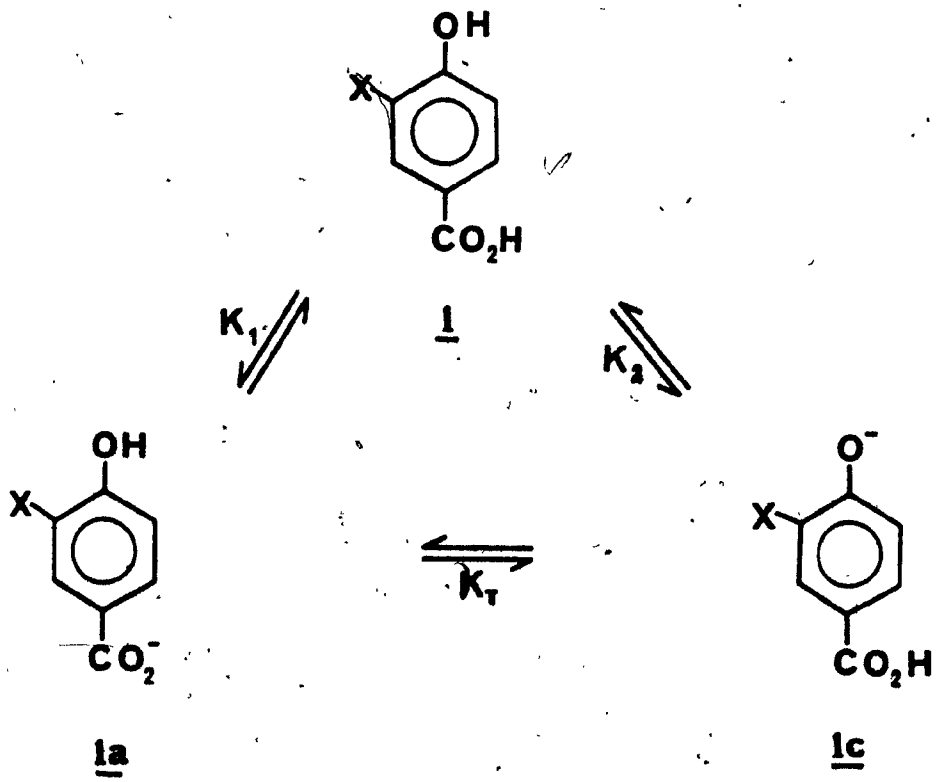
estimated pK_3 = 6.74 was arrived at using equation 52 and an appropriate σ constant

$$pK_a = 9.92 - 2.23 \Sigma \sigma \qquad (52)^{45}$$

for the ortho bromo substituent of 0.70.[47] From these values the estimated k_2''' is 3.3×10^9 $M^{-1}s^{-1}$ which is within the range of those observed for other phenoxides.[9-11, 42]

The tautomeric ratio (ic) / (ia) may be estimated from the Scheme 8.

Scheme 8



1a 1c

$$\therefore \quad K_T = \frac{(1c)}{(1a)} = \frac{K_3}{K_1}$$

Where $K_1 = 10^{-4.80}$ M and $K_3 = 10^{-8.30}$ M

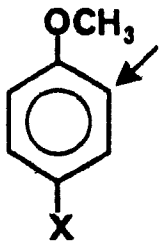
and so $K_3 / K_1 = 0.00032 = K_T$

The tautomer 1c is only present to an extent of 3 molecules in 10,000 but still the reaction proceeds via 1c because the k_2''' for 1c is 8.2×10^9 M^{-1} s^{-1} and k_2' for 1a is 2.8×10^5 M^{-1} s^{-1} i.e. 1c is 29,000 times more reactive than the predominant tautomer 1a.

The estimated tautomeric ratio for the 3-bromo-4-hydroxybenzoic acid (2) monoanion is 0.0017. This K_T value is larger because substituent effects on the acidity of phenolic hydroxy are larger (ρ = 2.23)[45] than on the ionization of carboxyl groups (ρ = 1.0). Therefore the tautomeric ratio has an effective ρ = 1.23 and so the electron-withdrawing substituent bromo increases the proportion of the minor tautomer. The unusual rate profile for 3-bromo-4-hydroxybenzoic acid (2) can be accounted for as being due to the high K_T value (0.0017) coupled with the high reactivity of 3-bromo-1c form ($k_2''' = 3.3 \times 10^9$ M^{-1} s^{-1}) over 3-bromo-1a form ($k_2' = 1086$ M^{-1} s^{-1}) i.e. the minor tautomeric anion in this case is about 3 million times more

Table VI

Rate Constants for the Bromination of p-Substituted Anisoles.

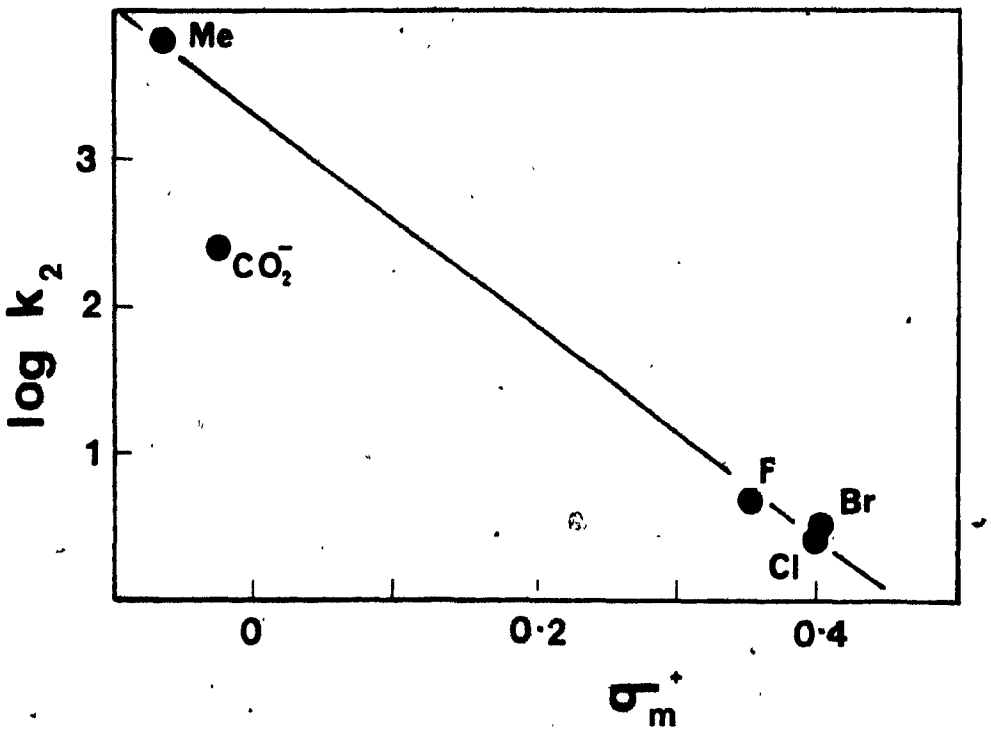


X	σ_m^+	k_2 ($M^{-1}s^{-1}$)	Ref / Note
Me	-0.066	6.2×10^3	41
CO_2^-	-0.028	260	a
F	0.352	5.2	41
Cl	0.399	2.7	41
Br	0.405	3.25	41

[a] From this study

Figure 3

$\sigma - \rho$ Plot for the bromination of p-substituted anisoles.



(intercept = 3.31 (+ 0.08), slope = -7.15 (+ 0.23) and r = .9989).

reactive than the major anion.

We now return to the comparison of the reactivities of the monoanions of p-hydroxybenzoic acid (1a and p-anisic acid (3a). The former is 10000 times more reactive towards bromine than the latter. From the above discussion it is established that 1a reacting via the minor tautomer 1c is 9.3 (Table V) times more reactive than expected, a truer ratio for reactivity of (1a)/(3a) would then be about 1110. Theoretically this ratio should be approximately 12 as the $\sigma_m^+ \sim 0$ for $-CO_2^-$ resulting in a similar ratio like phenol / anisole. This high ratio of (1a)/(3a) clearly indicates the low reactivity of 3a. From the σ-ρ correlation line for the aqueous bromination of other para-substituted anisoles[41] (Table VI and Figure 3) it is evident the point for $-CO_2^-$ is low by a factor of 13. Similar observations with respect to low reactivity with $-CO_2^-$ substituent have been reported. A similar feature is noted for o-substituted anisoles[41] (by a factor of 8.5) and 2-substituted furans[49] (by a factor of 48) in their correlations for the aqueous bromination of these substrates.

In all these cases the rates seem to fit the line if the value σ_m^+ for $-CO_2^-$ is $\simeq$ 0.10 rather than -0.028 as given in Hammett tables.[43] This value is close to σ_m =

0.09 based on the ionization of the substituted benzoic acid,[48] which seems reasonable (since $\sigma_m^+ \simeq \sigma_m$ in most cases). May be the σ_m^+ value for $-CO_2^-$ is incorrect or unreliable, as suggested by Hine,[50] due its charge.

Now, if $\sigma_m^+ = 0.10$ for $-CO_2^-$ is assumed to be more appropriate then the expected k_2' values for bromine reaction with 1a and 2a will be reduced to 42000 M^{-1} s^{-1} and 210 $M^{-1}s^{-1}$ respectively. In which case, the apparent rate constants for these anions will even be more elevated by a factor of 62 and 27000 respectively, instead of 9.3 and 5200 (Table V). Thus the proposed scheme for the reaction of p-hydroxybenzoic acid (1) and 3-bromo-4-hydroxybenzoic acid (2) reacting via their minor tautomers 1c and 2c would seem even more probable.

Summary:

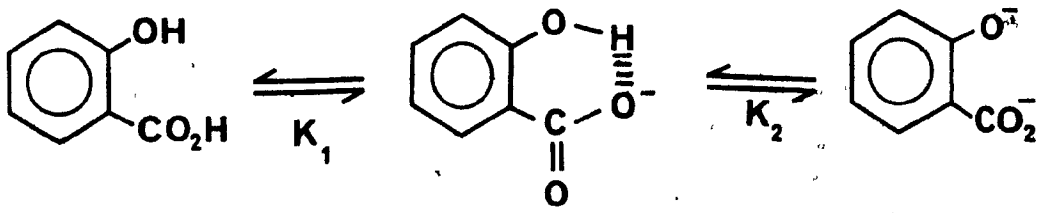
From the kinetics of the aqueous bromination of p-hydroxybenzoic acid (1) and 3-bromo-4-hydroxybenzoic acid (2) it is evident that the anions 1a and 2a have abnormally high reactivities. These can be attributed to their reaction occurring via their minor tautomeric anions 1c and 2c respectively. In addition, the p-anisate ion has a considerable low reactivity compared to other anisoles. This may be due

to an incorrect σ_m^+ value cited for $-CO_2^-$.

CHAPTER 3

Bromination of Salicylic Acid and its Derivatives

Salicylic acid (5) has abnormal pK_a values when compared to p-hydroxybenzoic acid (1). Its first and second pK_a's are 2.98 and 13.61[51], respectively, which are quite different from the corresponding values of p-hydroxybenzoic acid: 4.61 and 9.31[46], which are normal for a benzoic acid and a phenol, respectively.



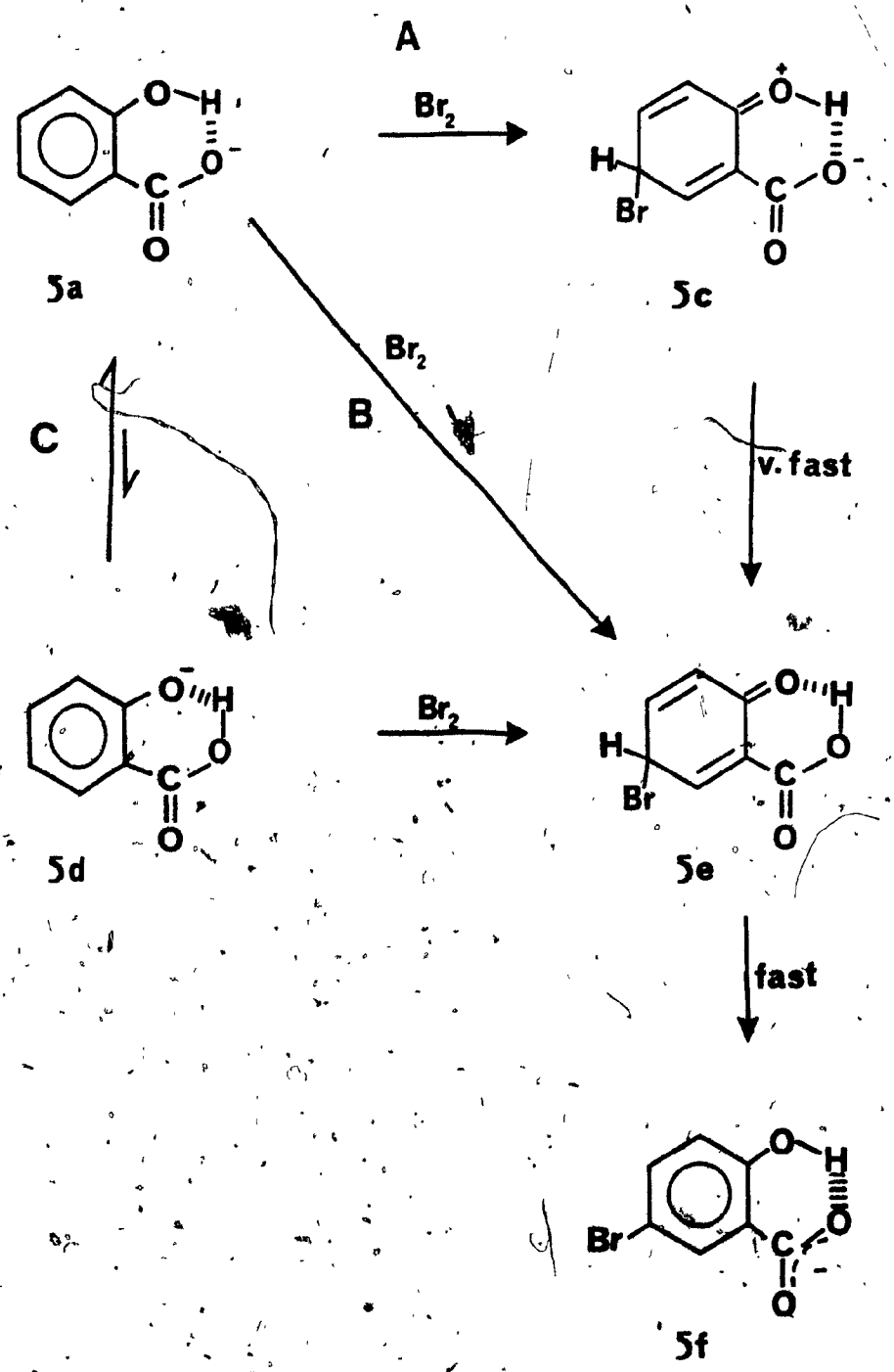
5 5a 5b

(11)

Furthermore, deprotonation of the salicylate monoanion (5a) by hydroxide ion is relatively slow ($k_{OH} \sim 10^7$ M^{-1} s^{-1}) for a phenol[52] and also the protonation of 5a by hydronium ion is slow for a carboxylate ion.[53]

These abhormalities are attributed to an intramolecular hydrogen-bond between the hydroxyl group and the

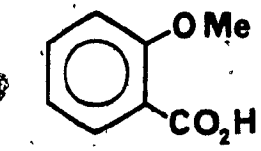
Scheme 9



carboxylate function of the salicylate monoanion 5a.[52,53] The recent work of Hibbert and Awwal[52] supports this idea; they have shown that the slow deprotonation of salicylate ion results from base attack at a normal rate upon a small equilibrium amount ($\sim$ 0.1%) of the monoanion 5a without the internal hydrogen-bond. This mechanism was suggested earlier by Eigen.[54]

The study of aqueous bromination of salicylic acid and its derivatives was carried out to determine the effect if any, of the intramolecular hydrogen-bond in 5a on the reactivity or reaction mechanism. The initial hypothesis for the bromination of 5a can be appreciated by reference to Scheme 9.

If the attack of bromine is normal via pathway A on the salicylate monoanion 5a, the zwitterionic intermediate 5c will be formed. This intermediate 5c has an highly acidic proton (pK < -3)[55,56] hydrogen-bonded to a basic carboxylate oxygen (pK $\sim$ 4) and therefore the intramolecular proton transfer to yield 5e will be very fast. If this proton transfer is sufficiently fast (10^{12} - 10^{13} s^{-1}) then the conversion of 5a to 5e may be a concerted process (pathway B) with the bromine attack and proton transfer occurring



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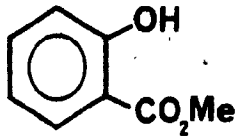

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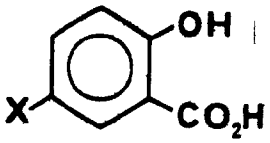

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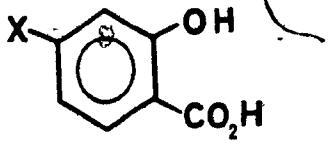


9

	X
(i)	Br
(ii)	SO_3H
(iii)	NO_2
(iv)	Me
(v)	CHO

	X
(i)	Cl
(ii)	Me

more or less simultaneously. Alternatively, the reaction might occur via the third pathway C where bromine attacks the minor tautomeric anion 5d to form 5e.

The carboxyl group in the cyclohexadienone intermediate 5e may facilitate the conversion of 5e to product 5f. This step is probably too fast to be observed since no evidence of a build-up of 5e was found. Therfore, this study is mainly concerned with the formation of the intermediate 5e.

Results:

The kinetics of bromination of salicylic acid (5), o-anisic acid (6), methyl salicylate (7), various 5-substituted salicylic acids (8i to 8v) and 4-substituted salicylic acids (9i and 9ii) in aqueous buffers in the pH range of 0-7 have been studied. Overall these substrates all exhibited second-order kinetics: first-order in substrate and first-order in Bromine at fixed pH. Accordingly, the observed

$$\text{rate} = k_2^{obsd} (S) (Br_2) \qquad (53)$$

first-order rate constants obtained in the presence of excess substrate were converted to second-order rate constants (k_2^{obsd}) with the necessary corrections made for

actual concentration of free bromine present in solution.

(i) Salicylic acid (5):

The second-order rate constants for this substrate are given in Table VII and the pH-rate profile is in Figure 4. The shape of the rate profile is as expected for the reaction upon the salicylate anion 5a, since the first pK_a of 5 is 2.98.[51] Thus the data can be represented by equation 33 where k_2 and k_2' are the rate constants for the attack of bromine upon the undissociated form 5 and the

$$k_2^{obsd} = \frac{k_2 (H^+) + k_2' K_1}{(K_1 + (H^+))} \qquad (33)$$

monoanion 5a respectively and K_1 is the first pK_a of 5. The fitted values of the parameters are $k_2 = 4650\ M^{-1} s^{-1}$, $k_2' = 3.28 \times 10^6\ M^{-1} s^{-1}$ and $K_1 = 1.32 \times 10^{-3}\ M$ ($pK_1 = 2.88$).

(ii) 4- and 5- Substituted salicylic acids (8 and 9):

Each set of data (Table VIII to XIII) for these substrates can be represented by equation 34 (except where X = $-NO_2$ and -CHO), as shown by the calculated curves for

$$k_2^{obsd} = \frac{k_2' K_1}{(K_1 + (H^+))} \qquad (34)$$

these substrates in Figures 5 and 6. The values of the para-

Table VII

Rate Constants for the Reaction of Bromine with Salicylic Acid (5).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
-0.30	5.93×10^{3} [g]
0.11	1.10×10^{4} [g]
0.43	1.92×10^{4} [g]
0.86	3.60×10^{4} [g]
1.02	6.79×10^{4}
1.26	6.50×10^{4} [c,g]
1.40	9.56×10^{4}
1.68	1.76×10^{5}
2.01	4.06×10^{5}
2.24	5.30×10^{5} [g]
2.41	6.79×10^{5}
2.57	1.29×10^{6} [g]
2.80	1.66×10^{6}
3.01	2.06×10^{6}
3.35	2.71×10^{6}
3.76	3.03×10^{6}
3.85	3.06×10^{6}

Table VII (Cont'd)

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
3.88	4.11×10^6 e
3.90	4.11×10^6 f
4.10	4.59×10^6 d
4.53	4.13×10^6 d
4.69	4.13×10^6 e
4.72	3.39×10^6 f
4.78	3.26×10^6
4.93	2.72×10^6
5.20	3.20×10^6
6.30	2.47×10^6
6.78	2.32×10^6

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (Salicylic acid) = 1×10^{-4} M; (Bromine) = 1×10^{-5} M.

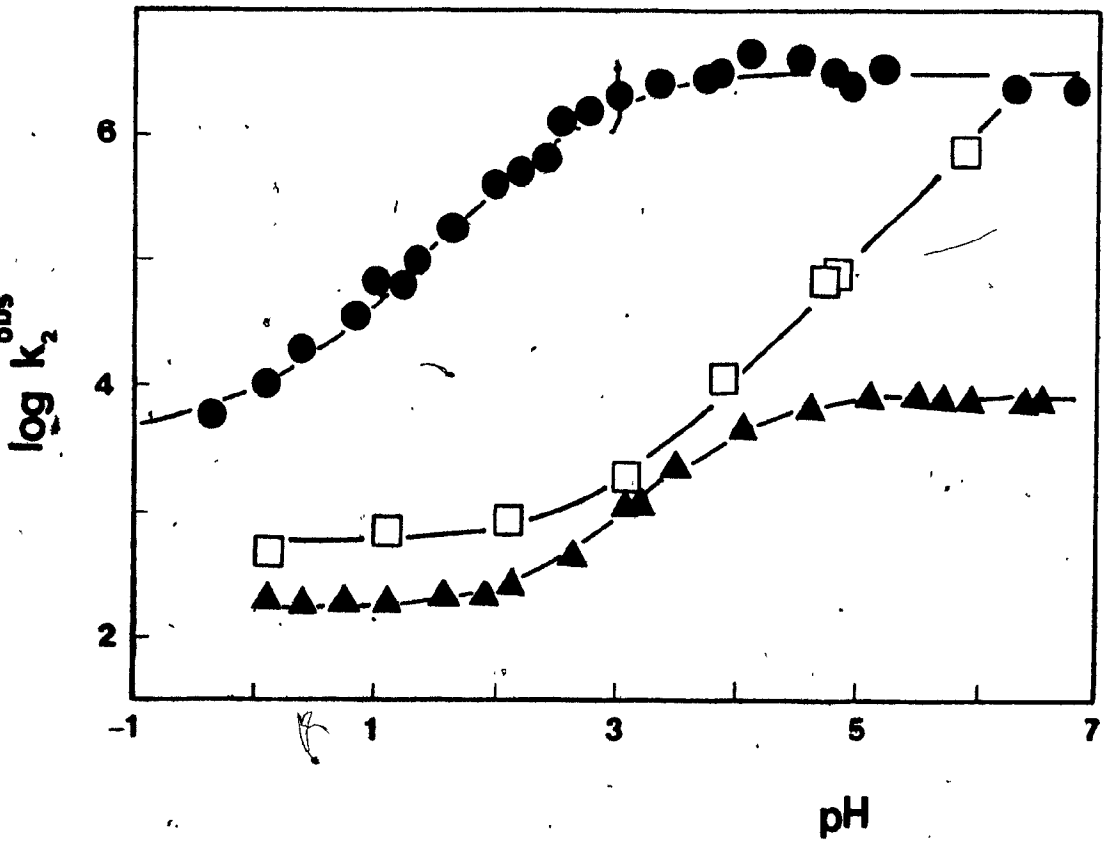
c. (Salicylic acid) = 5×10^{-4} M; (Bromine) = 5×10^{-5} M.

d. (Bromine) = 2×10^{-5} M. e. (Copper (II)) = 1×10^{-5} M.

f. (Iron (II)) = 1×10^{-5} M (e and f data not plotted).

g. Preliminary data obtained by B. Kraus.

Figure 4



Rate profiles for the bromination of salicylic acid (5) (●), methyl salicylate (7) (□) and o-anisic acid (6) (▲).

Table VIII

Rate Constants for the Reaction of Bromine with 5-Bromosalicylic Acid (8i).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
0.13	5.17×10^{2}
0.442	1.21×10^{3}
0.732	2.62×10^{3}
1.098	6.37×10^{3}
1.50	1.54×10^{4}
2.085	2.99×10^{4}
2.55	7.65×10^{4}
3.03	1.10×10^{5}
3.50	1.30×10^{5}
4.11	1.94×10^{5}
4.41	1.75×10^{5}
4.58	2.28×10^{5}
4.67	2.16×10^{5}
4.87	2.16×10^{5}
4.98	1.77×10^{5}
5.03	2.42×10^{5}
5.20	2.58×10^{5}

Table VIII (Cont'd)

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
5.41	2.19×10^5
6.33	2.15×10^5
6.84	1.98×10^5

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (5-Bromosalicylic acid) = 5×10^{-4} M; (Bromine) = 5×10^{-5} M.

Table IX

Rate Constants for the Reaction of Bromine with 5-Sulphosalicylic Acid (Sii).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
0.13	2.83×10^2
1.098	3.00×10^3
2.085	1.96×10^4
2.81	5.38×10^4
3.90	7.94×10^4
4.76	9.58×10^4
5.39	9.93×10^4

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (5-Sulphosalicylic acid) = 5×10^{-4} M;

(Bromine) = 5×10^{-5} M

Table X

Rate Constants for the Reaction of Bromine with 5-Nitrosalicylic Acid (8iii).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
0.13	1.55×10^2
1.098	1.69×10^3
1.611	4.50×10^3
2.085	8.26×10^3
2.47	1.20×10^4
2.77	1.39×10^4
3.18	1.42×10^4
3.89	1.63×10^4
4.29	2.04×10^4
4.71	2.13×10^4
5.07	3.21×10^4
5.93	9.04×10^4

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (5-Nitrosalicylic acid) = 5×10^{-4} M; (Bromine) = 5×10^{-5} M.

Table XI

Rate Constants for the Reaction of Bromine with 4-Methyl- and 5-Methylsalicylic Acid.[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
4-Methylsalicylic Acid (9ii)	
0.13	9.76×10^4
1.098	5.38×10^5
2.085	3.08×10^6
5-Methylsalicylic Acid (8iv)	
0.13	3.13×10^3
1.098	2.03×10^4
2.085	1.79×10^5
2.86	9.45×10^5
3.93	1.78×10^6
4.84	1.83×10^6
5.74	2.17×10^6

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (Substrate) = 1×10^{-4} M; (Bromine) = 1×10^{-5} M.

Table XII

Rate Constants for the Reaction of Bromine with 4-Chlorosalicylic Acid (9i).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
0.13	4.73×10^{3}
1.098	5.05×10^{4}
2.085	3.10×10^{5}
3.02	1.28×10^{6}
3.97	1.41×10^{6}
4.90	1.36×10^{6}
5.74	1.29×10^{6}

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. {4-Chlorosalicylic acid} = 1×10^{-4} M; {Bromine} = 1×10^{-5} M.

Table XIII

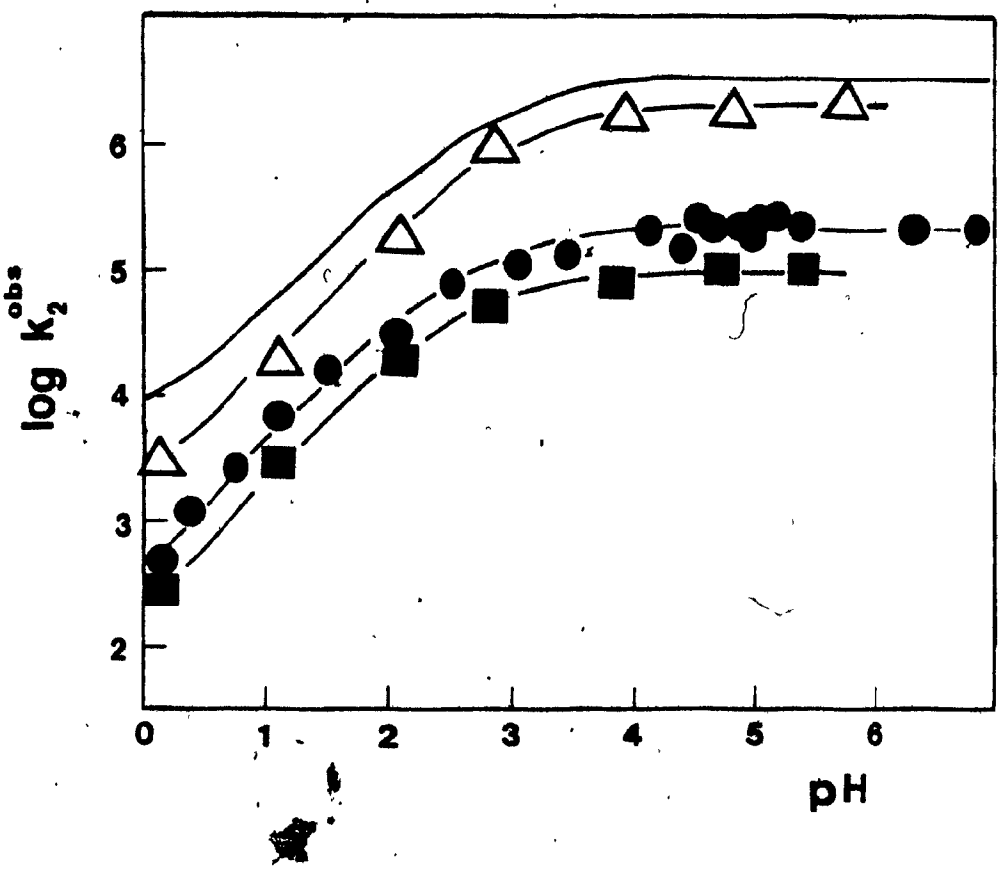
Rate Constants for the Reaction of Bromine with 5-Formylsalicylic Acid (8v).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
0.645	1.83×10^3
1.098	1.16×10^4
2.085	3.76×10^4
2.50	1.98×10^5
3.96	3.73×10^5
4.85	3.82×10^5
5.62	8.76×10^5

a. At 25 °C, in 0.1M KBr. The values for k_2^{obsd} are corrected for Br_3^- ion and HOBr formation.

b. (5-Formylsalicylic acid) = 5×10^{-4} M; (Bromine) = 5×10^{-5} M.

Figure 5



pH Rate profile for the bromination of 5-bromosalicylic acid (8i) (●), 5-methylsalicylic acid (8iv) (△) and 5-sulphosalicylic acid (8ii) (■).

meters obtained from fitting these data are listed in Table XVI. The pK_1 values obtained for these substrates are very close to the literature pK_a values indicating that the profiles for 5-bromo (8i), 5-sulpho (8ii), 5-methyl (8iv), 4-methyl (9ii) and 4-chloro (9i) salicylic acid are consistent with them reacting via their monoanions.

In case of 5-nitro (8iii) and 5-formyl (8v) salicylic acids in the pH range of 0-4.5 the rate profile is consistent with reaction upon its monoanion but above pH 4.5 there is an increase in rate and this may be due to the onset of reaction upon the dianion (similar to the case of p-hydroxybenzoic acid (1)). Therefore a better fit to the

$$\text{rate} = \frac{k_2' K_1}{(K_1 + (H^+))} + \frac{k_2'' K_2}{(H^+)} \qquad (54)$$

data for these two substrates is obtained by using equation 54 instead of 34 as shown by the calculated curve in Figure 6.

(iii) o- Anisic acid (6):

The pH-rate data for this substrate are given in Table XIV. From the rate profile (Figure 4) for this substrate it can be seen that at pH 0-2 the reaction is mainly via the undissociated form of 6 and at pH's >2 the attack of

Table XIV

Rate Constants for the Reaction of Bromine with o-Anisic Acid (6).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)	
0.11	2.20×10^{2}	c
0.43	1.90×10^{2}	c
0.77	1.91×10^{2}	c
1.12	1.78×10^{2}	c
1.60	2.01×10^{2}	c
1.92	2.04×10^{2}	c
2.10	2.49×10^{2}	d
2.64	4.47×10^{2}	d
3.07	1.21×10^{3}	d
3.26	1.74×10^{3}	d
3.48	2.42×10^{3}	d
4.07	4.47×10^{3}	d
4.61	6.89×10^{3}	d
5.08	8.44×10^{3}	d
5.47	8.54×10^{3}	c
5.68	9.04×10^{3}	d
5.90	8.37×10^{3}	d
6.40	7.79×10^{3}	c
6.49	8.46×10^{3}	d

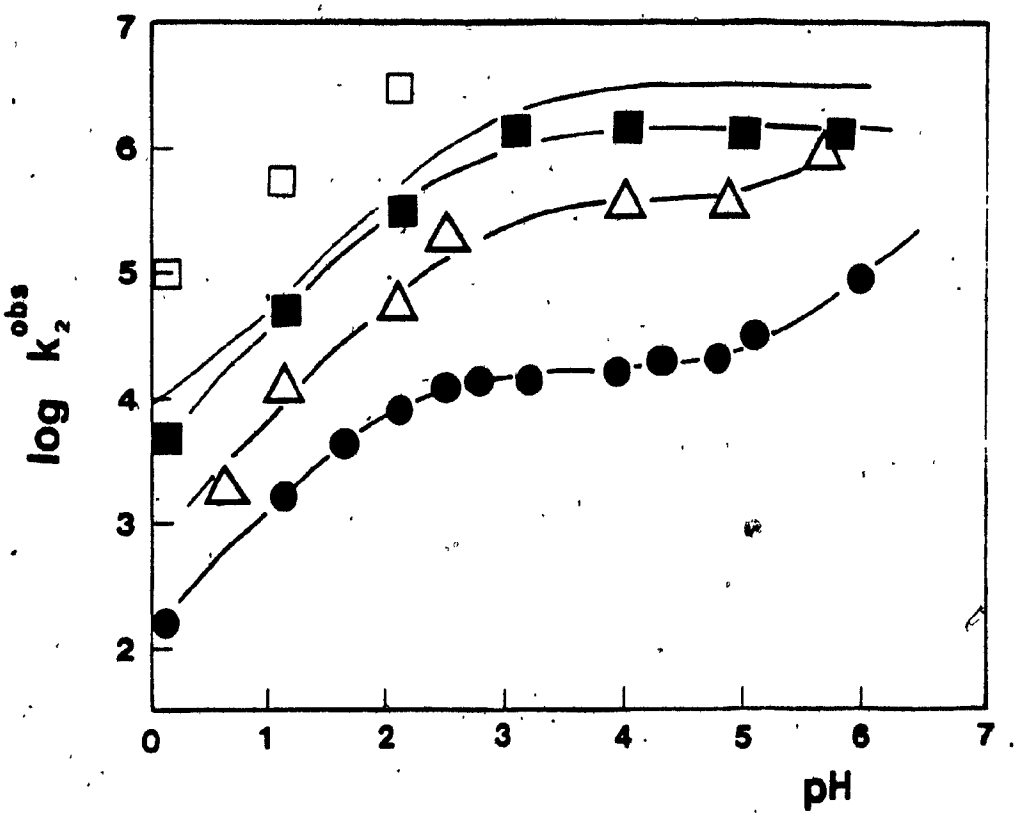
a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (o-Anisic acid) = 3×10^{-4} M; (Bromine) = 3×10^{-5} M.

c. (o-Anisic acid) = 5×10^{-4} M; (Bromine) = 5×10^{-5} M.

d. Preliminary data obtained by B. Kraus.

Figure 6



pH Rate profile for the bromination of 5-nitrosalicylic acid (8iii) (●), 5-formylsalicylic acid (8v) (△), 4-methylsalicylic acid (9ii) (□) and 4-chlorosalicylic acid (9i) (■).

bromine is upon its monoanion. The calculated curve in Figure 4 for o-anisic acid was obtained using equation 33 and the respective values of the parameters obtained by fitting to the data are as indicated in Table XVI. The fitted pK_a value for 6 is 3.99 and is very close to the literature value of 4.08.[46]

(iv) Methyl salicylate (7) :

The rate profile for methyl salicylate is similar to those of other monosubstituted phenols.[10,42] In the pH range of 0-2 the rate is invariant which is due to the attack of bromine upon the undissociated form of 7. At higher pH the rate increases gradually due to reaction via the phenoxide ion. The kinetic data are given in Table XV and the rate profile is shown in Figure 4. The data can be represented by equation 41 in which k_2 and k_2'' are the

$$k_2^{obsd} = k_2 + \frac{k_2'' K_2}{(H^+)} \qquad (41)$$

rate constants for the undissociated and dissociated forms of 7 respectively and K_2 is the dissociation constant of the phenolic hydroxyl. The values of the parameters are listed in Table XVI.

Table XV

Rate Constants for the Reaction of Bromine with Methyl Salicylate (7).[a,b]

pH	k_2^{obsd} ($M^{-1}s^{-1}$)
0.13	4.93×10^2
1.098	7.12×10^2
2.085	8.87×10^2
3.10	1.91×10^3
3.91	1.19×10^4
4.74	7.16×10^4
4.77	7.53×10^4
5.88	7.94×10^5

a. At 25 °C, in 0.1 M KBr. The values for k_2^{obsd} are corrected for tribromide ion and hypobromous acid formation.

b. (Methyl salicylate) = 5×10^{-4} M; (Bromine) = 5×10^{-5} M.

Table XVI

Kinetic Parameters for the Bromination of Salicylic Acid (5) and its Derivatives.

Substrate	k_2	k_2'	k_2''	pK_1	pK_2
5	4650	3.3×10^6		2.88	
				(2.98)[a]	(13.61)[a]
8 i		2.0×10^5		2.68	
				(2.62)[b]	
8 ii		9.2×10^4		2.62	
				(2.62)[a]	
8 iii		1.7×10^4		2.10	
				(2.05)[b]	
8 iv	791	2.07×10^6		3.08	
				(3.02)[c]	
8 v		3.82×10^5		2.76[d]	
9 i		1.4×10^6		2.58[d]	
6	176	8626		3.99	
				(4.08)[e]	
7	613		7.18×10^9		
					(9.87)[a]

Table XVI (Cont'd)

a. Reference 51.

b. Reference 57.

c. Reference 90.

d. Not available.

e. Reference 46.

(v) Effect of metal ions:

In the plateau region of the rate profiles (Fig 4) for salicylic acid (5) and 5-bromosalicylic acid (8) the data are scattered. This is mainly due to the rates being very fast and the pseudo first-order rate constants approaching the limits of the stopped-flow equipment ($\sim 150\ s^{-1}$). Also to permit the measurement of fast rates, the concentrations of substrate and bromine were lowered to 10^{-4} M and 10^{-5} M respectively in the case of salicylic acid as a result of which there was a smaller absorbance change during the reaction.

The other possibility for scattering of the data could be due to the presence of traces of metal ions as the salicylate ions form strong complexes with transition metal ions.[58] Under the conditions used for these experiments the probable source of metal ion impurity could be from KBr as the water used was deionized and distilled. Therefore experiments involving the addition of ferrous ion and cupric ion (10^{-5} M) at pH's 3.9 and 4.7 were carried out. The k_2^{obsd} values obtained for salicylic acid were in the range of $3.4 - 4.1 \times 10^6\ M^{-1}\ s^{-1}$ (Table VII[e,f]) and these are slightly higher than the fitted value for the plateau region ($3.3 \times 10^6\ M^{-1}\ s^{-1}$) but are within the range of the

individual rate constants ($3.06 - 4.59 \times 10^6$ M^{-1} s^{-1}) measured in this region.

It thus appears that the scattering of data are mainly due to the pseudo first-order rate constants approaching the limits of the stopped-flow instrument, as mentioned above.

(Vi) Solvent Isotope Effect:

Solvent isotope effect studies were carried out to obtain evidence that the conversion of 5a to 5e involves the concerted attack of bromine and intramolecular proton transfer. In deuterium oxide medium a deuteron will be involved in the "proton" transfer and a reduction in the rate may be observed.

As there is a lot of scatter in the data in the plateau region for salicylic acid (5), isotopic studies were carried out with 5-bromosalicylic acid (8i) where the scattering is less. From a set of solvent isotopic studies in pH (pD) region of 4.5 to 5.5 (Table XVII) the average value of k_2^{obsd} in H_2O is 2.17×10^5 M^{-1} s^{-1} (5 runs) and 1.30×10^5 M^{-1} s^{-1} (6 runs) in D_2O. These values result in a $k_{H_2O} / k_{D_2O} = 1.67$.

Table XVII

Data for the Solvent Isotope effect studies of 5-Bromo-salicylic Acid (8i).

pH	k_2^{obsd}	p(D)	k_2^{obsd}
4.11	1.96×10^{5}	4.35	1.24×10^{5}
		4.52	1.29×10^{5}
		4.70	1.32×10^{5}
4.67	2.16×10^{5}	5.16	1.41×10^{5}
4.87	2.16×10^{5}		
5.03	2.42×10^{5}	5.40	1.27×10^{5}
5.41	2.19×10^{5}	5.85	1.28×10^{5}
Average (5)	2.17×10^{5}	Average (6)	1.30×10^{5}

Average $k_{H_2O} / k_{D_2O} = 1.67$

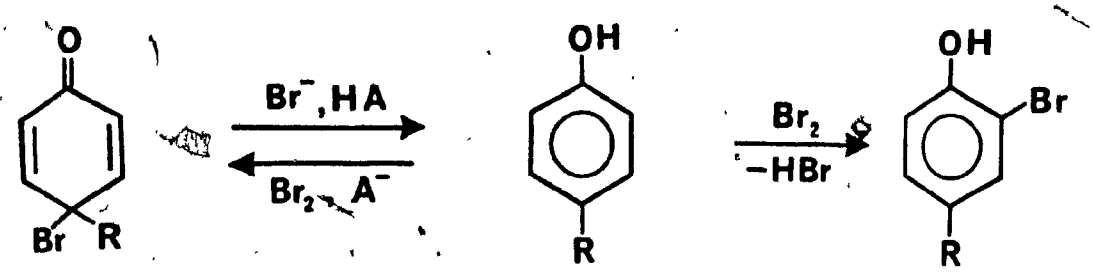
a. Units of k_2's are $M^{-1} s^{-1}$.

For comparison purposes solvent isotopic studies were carried out with o-anisic acid (6) as the substrate. At pH (pD) = 5.5 the k_{H_2O} / k_{D_2O} is 1.37.

(Vi) Cyclohexadienone intermediates:

As discussed elsewhere in this thesis, cyclohexadienone intermediates can be observed in phenol bromination in aqueous media. Therefore, attempts were made to observe the cyclohexadienone intermediate 5e from salicylic acid (see Scheme 9) but no such intermediate was observed. With p-alkyl phenols cyclohexadienones resulting from bromine attack ipso to the alkyl group have been observed, as discussed in Chapter 5 of this thesis. Thus a second attempt at the observation of intermediates was made with 5-methylsalicylic acid (8iv) and, indeed, the ipso-dienone of this substrate was observed. In the case of p-alkyl phenols it has been observed that the initial fast attack of bromine with the substrate is partitioned between ortho attack (~90%) and ipso attack (~ 10%). The ortho attack leads to the formation of ortho product 18 and the ipso attack gives observable dienone 16 which undergoes relatively slow decomposition by debromination (equation 55).[37] This process is bromide ion dependent and is catalyzed by H^+ and

buffer acids (see: Chapter 5 of this thesis).

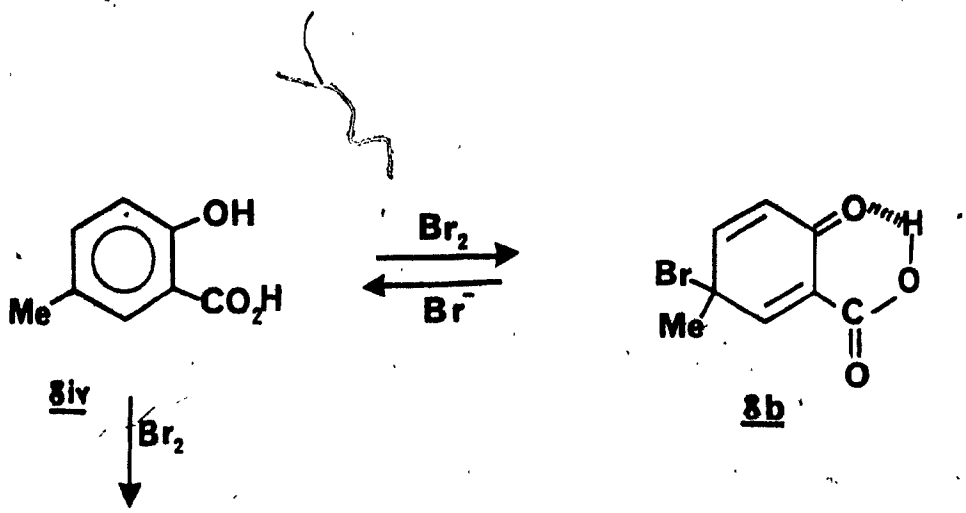


16 15 18

(55)

A similar type of reaction has been observed with 5-methylsalicylic acid (8iv). Bromine reacts fast with the anion of 8iv (Figure 5 and Table XVI) to produce a transient absorption at ~ 250 nm which is attributedd to the ipso-dienone 8b (Scheme 10). The decay of this ipso-dienone (8b) follows first-order kinetics and, similar to those from p-alkyl phenols, its decomposition is bromide ion dependent. The rate constants vary with pH as shown in Figure 7; the data are given in Table XVIII. Below pH 1.5 the rate of bromine attack is sufficiently slow that

kinetics for the decay of the ipso-dienone 8b could not be studied. Similar to the decay of ipso-dienones of p-alkyl phenols[37] the absorbance change for the decay of 8b was observed to be 10% of that expected if all the bromine reacted with 8iv to form 8b. The reaction of 5-methyl-salicylic acid with bromine to form ipso-dienone 8b and ortho product can be represented by Scheme 10.



Scheme 10

The pH-rate profile (Figure 7) ascribed to the decay of 8b is kinetically ambiguous. It could be due to a reac-

Table XVIII

Rate Constants for the Debromination of the Ipso-Dienone of 5-Methylsalicylic Acid (8 iv).[c]

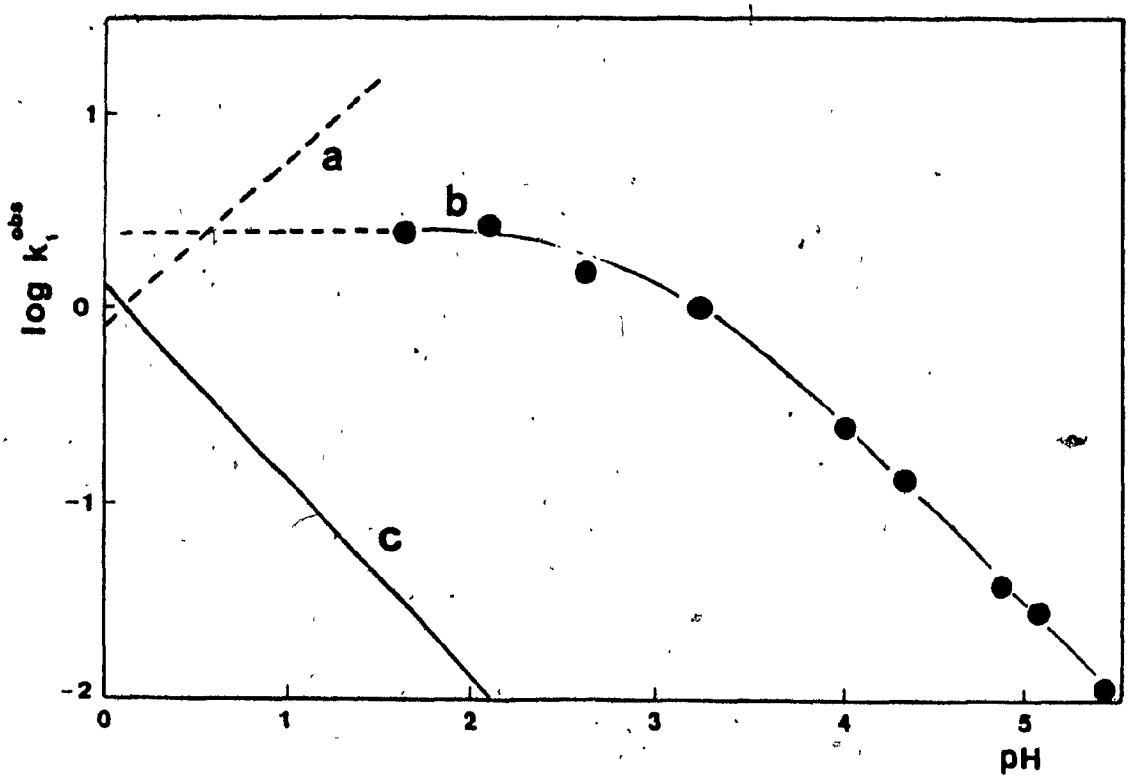
pH	k_1^{obsd}
1.61	2.58[b]
2.09	2.73[b]
2.62	1.57[b]
3.22	1.03[a]
3.98	0.260[a]
4.32	0.135[a]
4.85	0.040[a]
5.07	0.029[a]
5.41	0.012[a]

a. $(S) = 5 \times 10^{-4}$ M; $(Br_2) = 10^{-4}$ M.

b. $(S) = 10^{-3}$ M; $(Br_2) = 10^{-4}$ M.

c. At 25 °C, in 0.1M KBr.

Figure 7



(a) pH dependence of the pseudo first-order rate constant for bromine attack on 8iv under the conditions employed for the measurement of profile (b).

(b) pH-rate profile for the debromination of the ipso-dienone (8b) derived from 5-methylsalicylic acid (8iv) in 0.1M aqueous KBr.

(c) pH dependence of the pseudo first-order rate constant for the debromination of the ipso-dienone 15 (R = Me) derived from p-cresol, also in 0.1M aqueous KBr.

tion of the free acid form (Equation 56) or to a proton-catalyzed reaction of the conjugate anion (Equation 57).

$$k_1^{obsd} = k_1 (H^+) / (K_1 + (H^+)) \qquad (56)$$

$$k_1^{obsd} = k_2 K_1 (H^+) / (K_1 + (H^+)) \qquad (57)$$

If the reaction is due to the free acid the k_1 value (fitted) is 2.59 s^{-1} and if it is due to the conjugate anion the k_2 value is 3010 M^{-1} s^{-1}. In either case the fitted pK_1 value for 8b is observed to be 3.06. The decision between which of these is most probable is dealt with in the discussion section.

Ipso-dienones derived from p-alkyl phenols exhibit general acid catalysis, as shown later. However, in the case of decomposition of the ipso-dienone 8b no buffer catalysis was found.

Discussion:

The main point of interest to note from the rate profiles of these substrates is that the rate profile for salicylic acid (5) except for 9ii is above all other substrates of this group (unlike the p-hydroxybenzoic acid (1) and its derivatives). The second point is that the rate

profile for o-anisic acid (6) is well below that of salicylic acid (5), similar to the case of p-hydroxybenzoic acid acid (1) and p-anisic acid (3). To be more precise regarding reactivity, the anion of o-anisic acid (6) is 380 times less reactive than the salicylate monoanion (5a). Another point to note is the rate profile for methylsalicylate (7) is lower than the parent salicylic acid (5) again different from p-hydroxybenzoic acid (1) and its ethyl ester (4). In the case of 4-methylsalicylic acid (9ii) the rate profile is incomplete as at higher pH (> 2) the pseudo first-order rate constants obtained were not reliable because they were higher than can be measured by the stopped-flow apparatus (k_1 > 150 s^{-1}).

The reactivity of a salicylate anion can be compared with the reactivity of phenol as the σ^-_m for CO_2^- is -0.028[43] which is very close to zero. The rate constant for the attack of bromine on salicylate anion (5a) is 3.3×10^6 M^{-1} s^{-1} (Table XVI) whereas that for phenol is 4.2×10^5 M^{-1} s^{-1}.[10,37] The ratio of these is only 7.9 and may not be significant. However, if the comparison is made between the less reactive 5-nitrosalicylate anion (k_2 1.7×10^4 M^{-1} s^{-1} (Table XVI)) and p-nitrophenol (k_2 being < 60 M^{-1} s^{-1})[42] the difference in the reactivity is high by a factor of

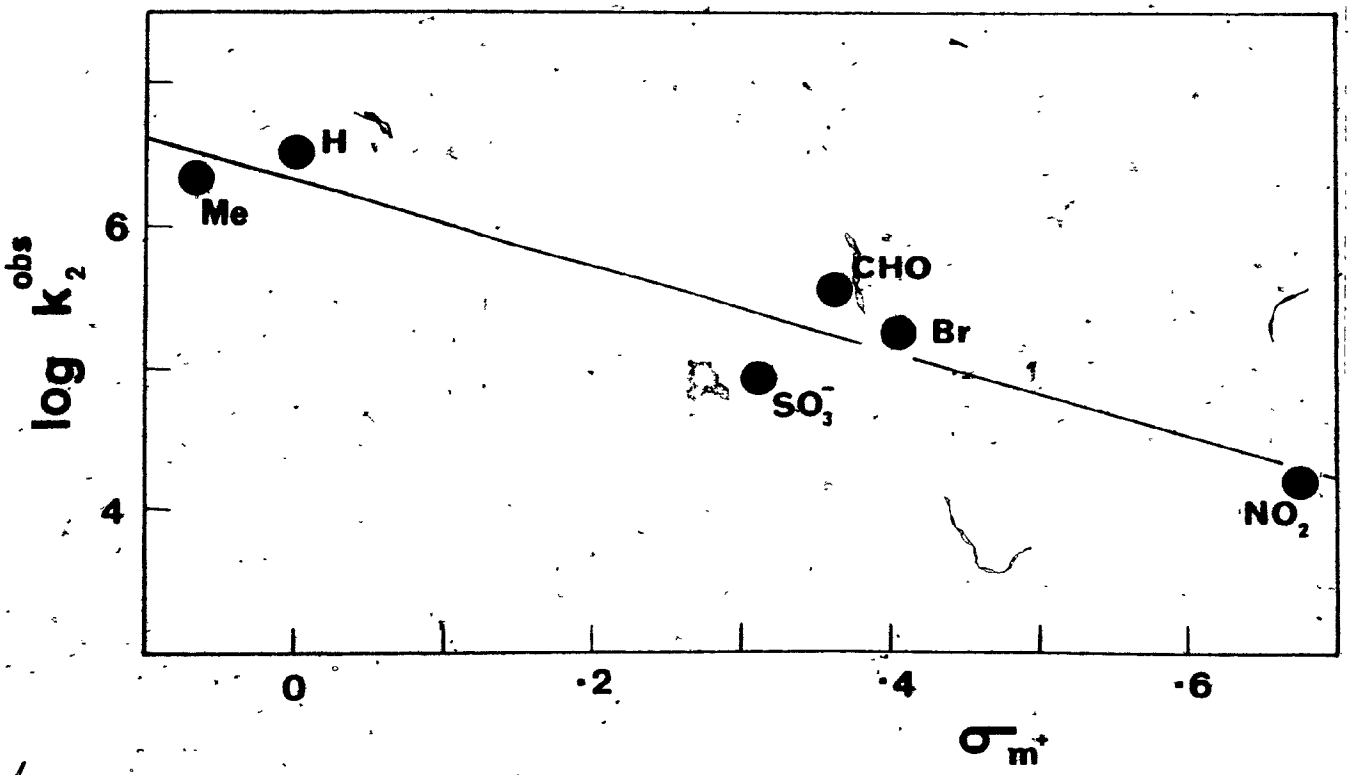


Figure 8 Hammett plot for 5-substituted salicylic acids.

(Slope = -2.94 and r = 0.94).

> 2800.

The difference in their reactivity can be better expressed using Hammett plots. The k_2' values of salicylic acid and 5-substituted salicylic acids (Table XVI) give a reasonable Hammett plot (Figure 8) with a correlation of 0.94 and $\rho^+ = -2.94$. However for the same type of plot for phenol and p-substitued phenols (Figure 2, Chapter 2) the ρ^+ value obtained is -5.21 (r = 0.98). This difference in the ρ value confirms that the effect of substituents is much less in 5-substituted salicylic acids than in p-substituted phenols. This eliminates the conventional pathway A in Scheme 9 for the bromination of salicylate monoanion. In this pathway the attack of bromine occurs on the intramolecularly hydrogen-bonded salicylate monoanion (5a) to give 5c which still has the phenolic hydroxyl with a positively charged oxygen and so the effect of 5-substituents should be essentially the same as in the case of p-substituted phenols.

Comparing the reactivity of salicylate monoanion (5a) and the anion of o-anisic acid (6) the latter is 380 times less reactive towards bromine compared to the former. In contrast anisole is only 12 times less reactive than phenol.[41] This supports the idea that 5a is more reactive

than phenol.

For consideration of pathway C in Scheme 9 , which is reaction via the minor tautomer 5d, the reactivities of salicylate monoanion (5a) and the anion of its methyl ester (7) can be compared where pH < pK_1 < pK_2. From the pH-rate profile (Figure 4) it is clear that their reactivities are quite different, unlike the case of the p-hydroxybenzoic acid anion (1a) and the anion of its ethyl ester (4) for which the profiles lie one on top of the other (Chapter 2).

Pathway C can be represented by Scheme 11 and for this the expected form of the observed rate constant is

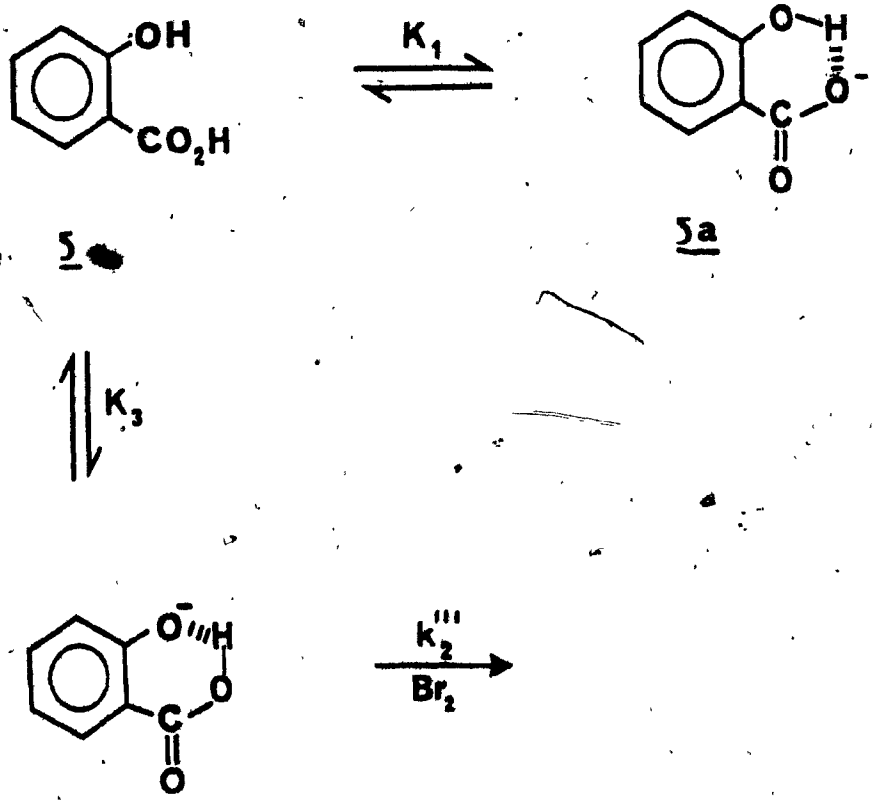
$$k_2^{obsd} = k_2''' K_3 / (K_1 + (H^+)) \qquad (50)$$

This, of course, is kinetically indistinguishable from the reaction via the major anion 5a for which

$$k_2^{obsd} = k_2' K_1 / (K_1 + (H^+)) \qquad (34)$$

From fitting to the observed data for salicylic acid $k_2' K_1 = 4350\ s^{-1}$, which can be equated to $k_2''' K_3$ (cf Equations 50 and 34). Since neither k_2''' nor K_3 are easily accessible the k_2''' will be assumed to be equal to k_2'' for the anion of methyl salicylate. This equals $7.2 \times 10^9\ M^{-1}\ s^{-1}$ (Table XVI), which is essentially diffu-

Scheme 11



5

5a

5d

sion-controlled, as observed for other monosubstituted phenoxide ions.[9-11, 39] Using this value for k_2''' leads to a calculated value of pK_3 = 6.31 which seems to be very unreasonable for the phenolic hydroxyl of 5. The low pK_3 value is a very clear indication that reaction via the minor tautomer 5d is improbable. Furthermore if k_2''' is lower than diffusion-controlled due to the stabilizing effect of the internal hydrogen-bond in 5d the pK_3 would be lower still.

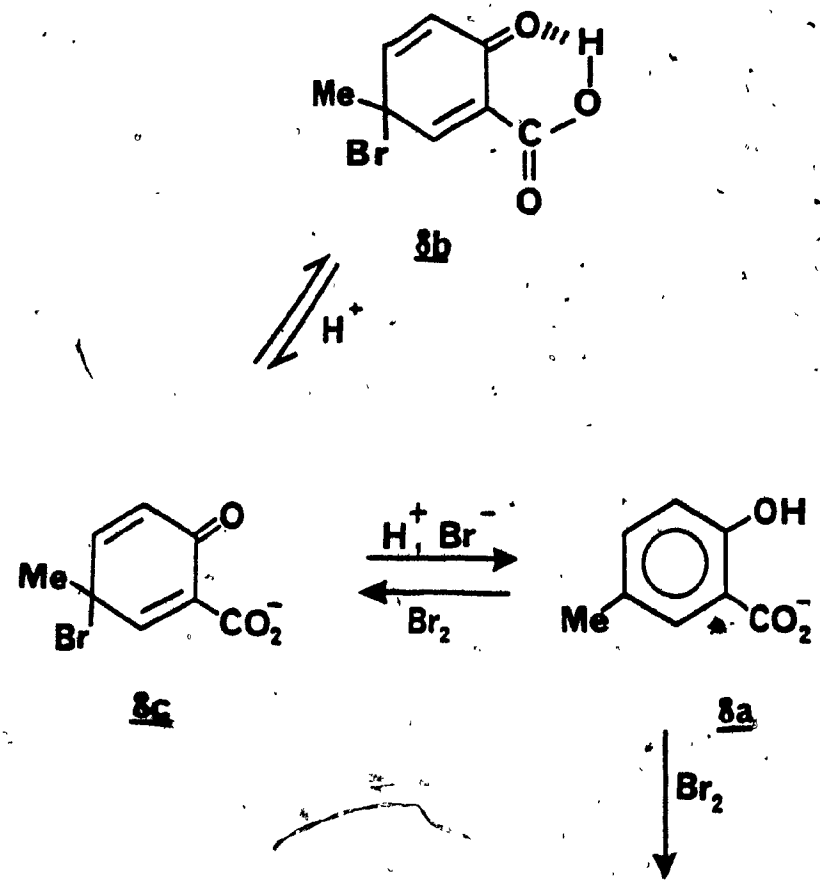
Overall if the reaction were to occur via 5d electron withdrawing substituents should increase the apparent reactivity of salicylate ions. But the ρ value from the present data for salicylate ions is -2.94 which is a further proof that the reaction via 5d is unlikely. From the above arguments regarding the low pK_3 value, ρ value of -2.94 and pH-rate profiles (figure 4) pathway C can be rejected.

This leaves with the choice of only the concerted pathway B in Scheme 9 for the bromination of salicylate monoanion where the intramolecular proton transfer limits the build-up of positive charge and so ρ^+ has a reduced value of -2.94. Solvent isotope effect studies were carried out in the hope that these results might contribute to the above arguments. For 5-bromo salicylic acid ion reaction in D_2O reduced the rate by a factor of 1.67 and for o-anisate

ion by 1.37. These low solvent isotope effects can be attributed to (i) the effect operating on the leaving group (bromide ion) since similar values (1.2 - 1.4) have been observed for solvolyses[59] and in alkene and alkyne brominations[60] (ii) the proton in flight at the transition state. It should be noted that low solvent isotope effects have been reported for other reactions involving intramolecular proton transfers.[61] Thus the k_{H_2O} / k_{D_2O} values obtained in this study are not inconsistent with pathway B but are not enough to confirm it.

Much stronger support for this pathway arises from the ipso-dienone 8b obtained from the bromination of 8iv. The decomposition of this ipso-dienone can be represented equally by equation 56 or 57 and which is more probable will be clear from the following arguments.

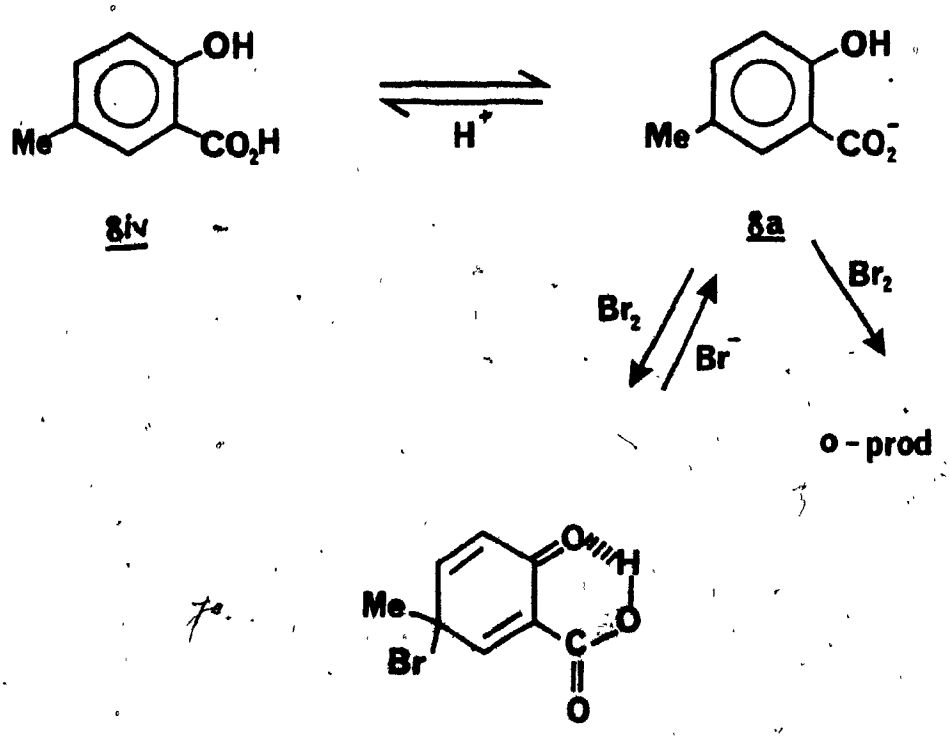
The ipso-dienone of p-cresol has the second-order rate constant (k_2) for the decomposition in 0.1M KBr of 1.3 $M^{-1}s^{-1}$ (Figure 7C) whereas for the dienone 8b if it reacts via its anion (equation 58), k_2's value is 2300 times greater. This seems unreasonable for the effect of a m-CO_2^- on these processes. The σ_m^+ for $-CO_2^-$ is ~ 0, as mentioned earlier, which means the presence of $-CO_2^-$ should have



(58)

little effect on the rate. An electrostatic effect (factor of ~ 10)[53,54,72] due to the negative charge on the anion 8c which would facilitate the attack of H_3O^+ can be expected but this should be nullified by an inhibitory effect on the attack of Br^-. Not only that, if 8b reacted via its anion 8c, buffer catalysis would be expected. As mentioned in the results section no such catalysis was observed for the decomposition of ipso-dienone 8b.

Scheme 12



8b

From the above discussion it seems that the ipso-dienone 8b reacts as the free acid form and the carboxyl group acts as an intramolecular general acid catalyst. The most probable rate equation for the decomposition of this ipso-dienone is S6 and the whole process can be represented by Scheme 12.

For the intramolecular process an effective molarity (EM)[62] of the internal carboxyl catalyst of 8b can be calculated. From the buffer catalysis studies of decomposition of the ipso-dienone 16 (R = Me) (discussed in Chapter 5) a Bronsted $\alpha \sim 0.13$ has been estimated. The pK_a of 8b acid is 3.06 and the predicted k_2 in 0.1M KBr (aqueous) is 0.306 M^{-1} s^{-1}. But the observed k_1 for 8b is 2.59 s^{-1} and therefore EM is 8.5M. This value is comparable to the values reviewed by Kirby for intramolecular general acid catalysis.[62] From this it can be said that the internal carboxyl in 8b catalyzes the debromination of 8b by bromide ion (Scheme 12). Then the formation of the ipso-dienone 8b should be catalyzed by the COO^- group in the ipso attack of bromine according to the Principle of Microscopic Reversibility. This is completely analogous to pathway B in Scheme 9 for the bromination of salicylate monoanion and this is further strong evidence for the proposed concerted pathway B.

Summary:

Based upon relative reactivities the bromination of salicylate anion and its derivatives most probably follows the concerted pathway (B in Scheme 9) rather than via the minor tautomer (pathway C) or via the protonated cyclohexadienone intermediate (pathway A). Supporting evidence for this concerted mechanism is given by the behaviour of the ipso-dienone 8b generated from 5-methylsalicylic acid (8iv). This dienone undergoes debromination as the free acid and the carboxyl group functions as an intramolecular general acid catalyst (Scheme 12) just as the debromination of the ipso-dienone from p-cresol (15) involves an external general acid catalyst. From this it can be deduced that the formation of ipso-dienone (8b) from 5-methylsalicylic acid must be catalyzed by the COO^- moiety of 8a (Scheme 12) according to the Principle of Microscopic Reversibility. The formation of the ipso-dienone is analogous to the concerted pathway B in Scheme 9 except that instead of a 5-methyl there is the 5-H in salicylic acid.

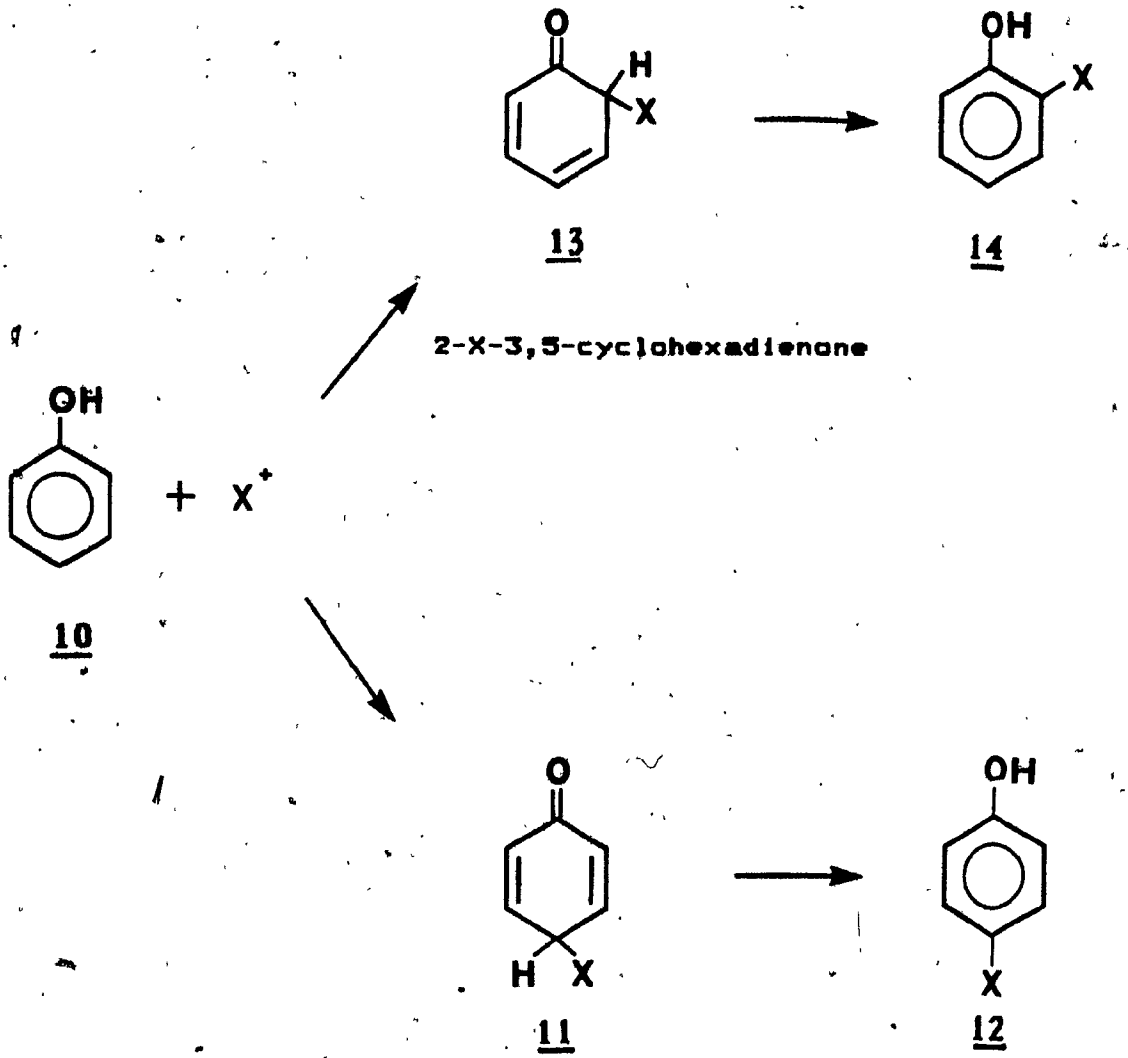
CHAPTER 4

Enolization of Transient Cyclohexadienones

Cyclohexadienones are tautomers of phenols, but such tautomerism has not been observed directly in simple phenols. With several 2,6-disubstituted or 2,4,6-trisubstituted phenols the cyclohexadienone intermediates have been observed by various groups of researchers[3,14,19-22] from reactions with electrophilic reagents, especially in halogenation of phenols. It is generally accepted that in electrophilic substitutions of phenol an intermediate 4-X-2,5-cyclohexadienone (11) or 2-X-3,5-cyclohexadienone (13) is formed initially which subsequently rearranges to the energetically preferred aromatic substituted phenol (Scheme 13). These cyclohexadienone type of intermediates are reasonably stable and have been detected in dilute solutions in acetic acid by spectroscopic methods in the past.[14,18,20,21] However, such type of intermediates were not observed earlier with simple phenols in aqueous solution

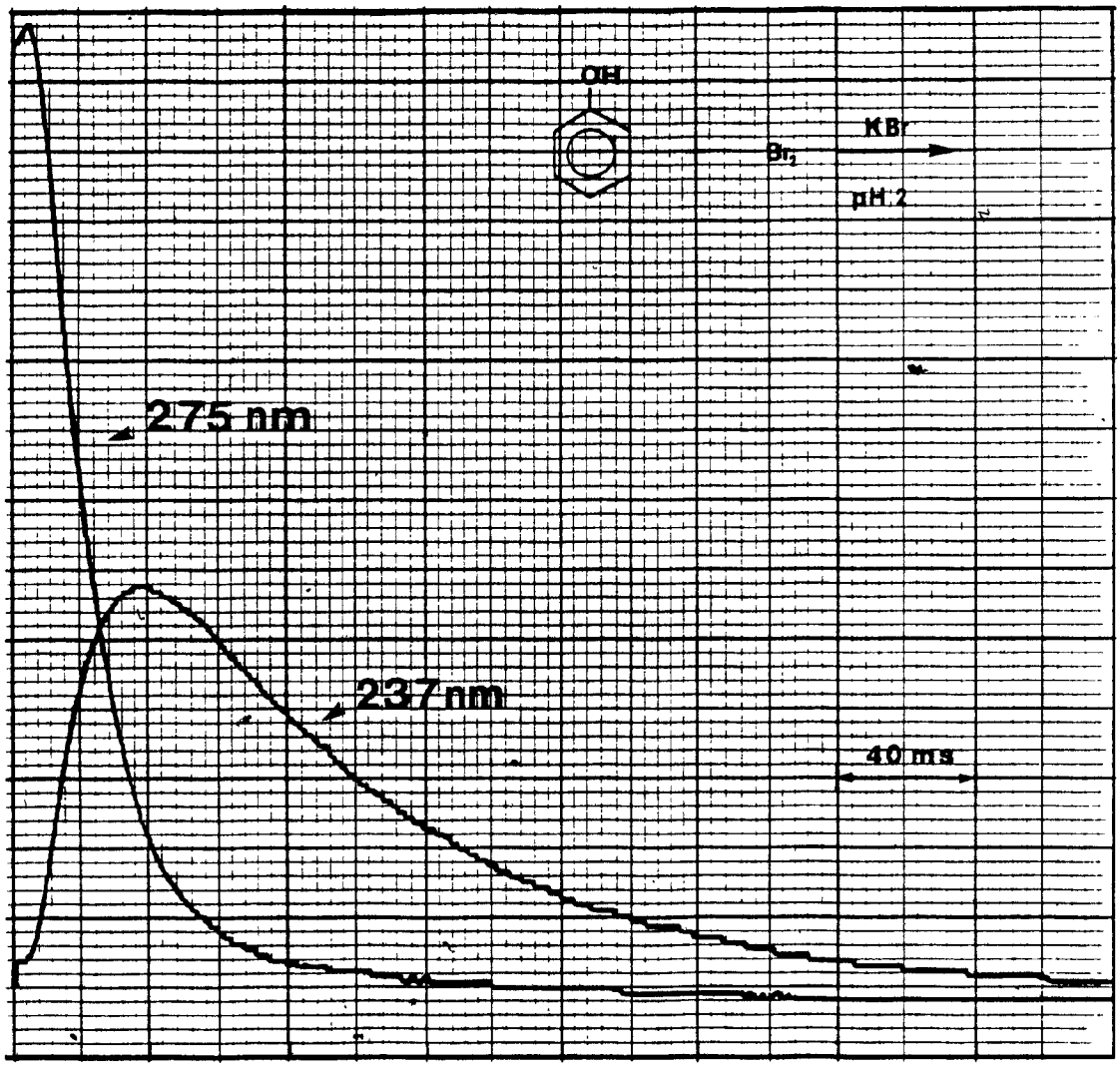
During an attempt to determine the rate of bromination of phenols at 0.1M ionic strength it was observed that when the reaction was monitored at 270-275 nm a decrease in the absorbance was observed which can be attributed to the disappearance of bromine (tribromide ion

Scheme 13



maximum being at 267 nm).[40] But when the reaction was monitored at 230-250 nm there was a considerable initial increase in absorbance followed by a slower decrease as shown in Figure 9. The reaction at 270-275 nm is due to the phenol reacting with bromine, the second-order rate

Figure 9: UV absorbance traces obtained during the aqueous bromination of phenol. Reaction conditions (phenol)=5×10^{-4}M, (Br_2)=5×10^{-5}M, pH 2, 0.1M KBr, at 25 ^{o}C.



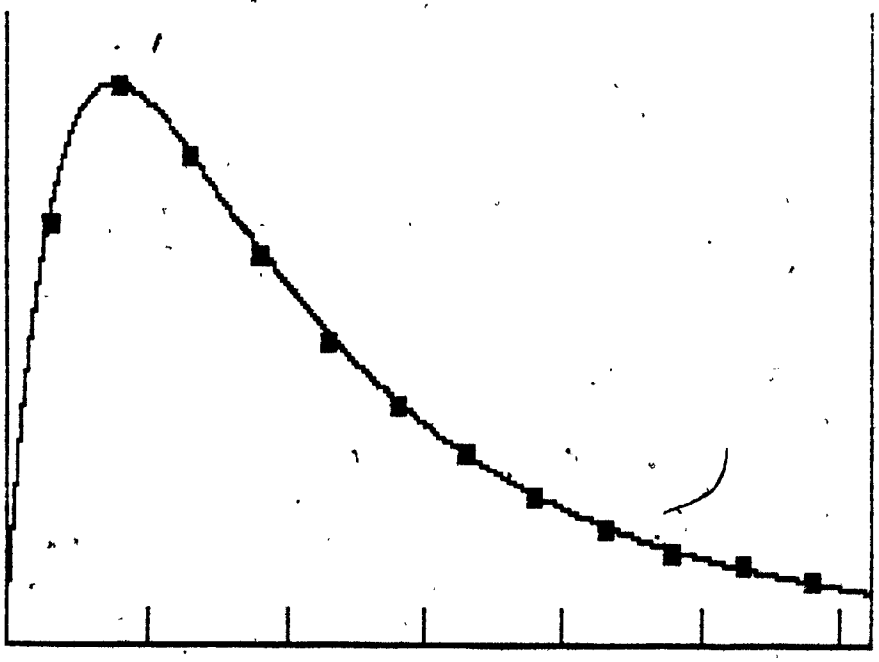
constants being 4.2×10^{5} M^{-1} s^{-1}.[10] The reaction observed at 230-250 can be ascribed to the formation and decay of the 4-bromo-2,5-cyclohexadienone (11) since various substituted 4-X-2,5-cyclohexadienones have absorption maxima in the region of 240-260 nm[3,20,21,56,63] whereas the 2-X-3,5-cyclohexadienones (13) have an absorption maxima around 310 nm.[64-67] The form of trace obtained (Figure 9) at 237 nm is appropriate to the first-order build-up and decay of a transient intermediate.[68] From Figure 9 it is also evident that the rate of the initial increase at 237 nm matches the decrease observed at 275 nm. The extent of increase in absorption at 237 nm depends upon the concentration of the limiting reagent (bromine). The apparent extinction coefficient obtained for the intermediate was 9000, in the same range as observed by the earlier groups[20,21,56,63] for 2,5-cyclohexadienones. The same type of trace which has been observed at 237 nm was computer simulated (Figure 10) using the following equations.[68] For process

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

$$\frac{dA}{dt} = -k_1 A \qquad \text{(ia)}$$

$$\frac{dB}{dt} = k_1 A - k_2 B \qquad \text{(ib)}$$

Figure 10: Computer simulated curve for the build-up and decay of 4-bromo-2,5-cyclohexadienone (11). The curve is calculated; the points are taken from the experimental trace in Figure 9.



$$\frac{dC}{dt} = k_2 B \qquad \text{(ic)}$$

Equation (ia) integrates to

$$A = A_0 e^{-k_1 t} \qquad \text{(ii)}$$

Substituting this into (ib) gives

$$\frac{dB}{dt} = k_1 A_0 e^{-k_1 t} - k_2 B \qquad \text{(iii)}$$

If $B_0 = 0$ then integration of (iii) leads to

$$B = \frac{A_0 k_1}{k_2 - k_1} \left(e^{-k_1 t} - e^{-k_2 t} \right) \qquad \text{(iv)}$$

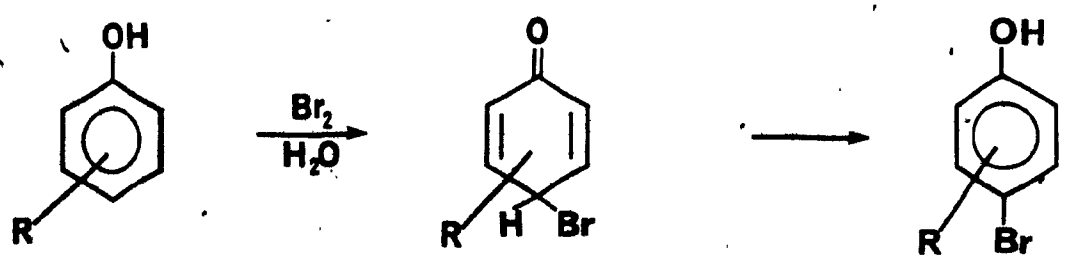
Using rate constants of $k_1 = 68\ s^{-1}$ and $k_2 = 14\ s^{-1}$ and an apparent extinction coefficient for the intermediate of 8900 the curve in Figure 10 was generated.

Results:

(A) Decomposition of 4-bromo-2,5-cyclohexadienones:

Studies were carried out to observe the decay of 4-bromo-2,5-cyclohexadienone formed from the reaction of bromine with phenol (10a), o-cresol (10b), m-cresol (10c), 2,6-dimethylphenol (10d), 3,5-dimethylphenol (10e) and 2,5-dimethylphenol (10f). The stopped-flow technique was used to generate the intermediates and to monitor their decay at 240-260 nm in aqueous media pH 0-6. The reaction can be

represented as in equation 59.



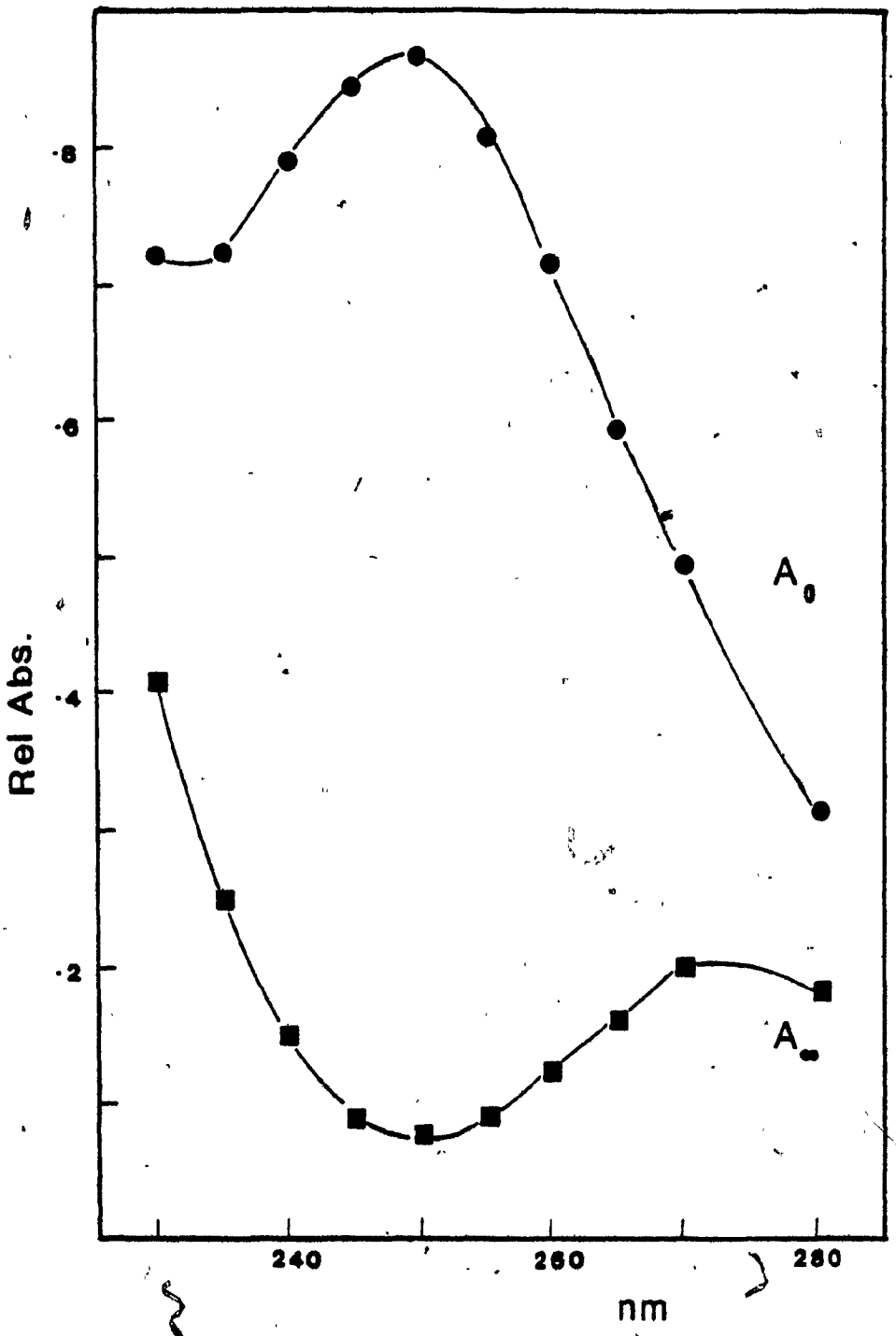
10 11 12

(59)

	R		R
a	H	d	2,6-diMe
b	2-Me	e	3,5-diMe
c	3-Me	f	2,5-diMe

Under the conditions used (ten-fold or five-fold excess of substrate) bromination of phenol leads predominantly to the formation of p-bromophenol (82%)[10] and seems to be the dominant pathway for the other phenols also. Analysis of the latter part of the decay curves for the intermediates gave first-order rate constants independent of

Figure 11: Initial and final absorbance values obtained from decay traces for the dienone (11d).



substrate, bromine or bromide ion concentrations as expected for irreversible formation of the cyclohexadienones (11). Of these, the dienone 11d derived from 10d was easiest to observe. With 2,6-dimethylphenol (10d) the attack of bromine is faster while the decay of the corresponding 4-bromo-2,5-dienone (11d) is much slower and therefore the absorbance traces for the decay of 11d were the best for analysis purposes. Figure 11 shows the initial and final absorbances obtained from the decay curve 11d at various wavelengths (at pH 3.42, (substrate) = 1×10^{-4} M, (bromine) = 1×10^{-4} M, 0.1M KBr, at 25°C). The figure shows a clear maximum at 250 nm and an extinction coefficient of 8000 which is consistent with the coefficients observed earlier for intermediates similar to 11d.

The reaction represented in equation 59 is the principle pathway under the conditions used for these reactions. The 2-bromo-3,5-cyclohexadienone (13) which is the corresponding intermediate in the formation of the minor o-bromo product was not detected. Such dienones have maxima around 310 nm and have a smaller extinction coefficients.[64-67] These 2-bromo-3,5-cyclohexadienones are most probably not detected because of their less stable nature,[22,69] undergoing very fast enolization to form the

Table XIX

Rate Constants for the Decay of the 4-Bromo-2,5-cyclohexadienone Intermediates Formed During the Brominations of Phenol (10a), o-Cresol (10b), m-Cresol (10c), 2,6-Dimethylphenol (10d), 3,5-Dimethylphenol (10e) and 2,5-Dimethylphenol (10f).[a]

Compound	pH	k_1^{obsd} (s^{-1})[b]
10a[b]	0.00	130.8[c]
	0.52	49.3[c]
	1.00	26.4
	1.92	16.0
	2.00	16.1
	2.60	15.5
	3.07	15.5
	3.41	14.9
	3.53	13.2[d]
	3.91	18.5
	4.25	18.6
	4.91	17.2
	6.03	19.8
10b[d]	0.00	60.4
	0.52	16.8
	1.00	6.95[b]
	2.12	3.07
	3.14	2.98
	4.83	3.71

Table XIX (Cont'd)

Compound	pH	k_1^{obsd} (s^{-1})
	4.91	3.76
	5.65	3.21
10c[b]	0.52	115[d]
	1.00	52.1[d]
	1.52	20.1
	2.00	11.7
	2.96	9.35
	4.03	10.5
	4.90	10.7
	6.09	10.9
10d[d]	0.00	4.04
	1.00	0.761[b]
	2.00	0.514[b]
	3.04	0.507
	3.13	0.502[b]
	3.42	0.511[b]
	3.93	0.664[b]
	4.31	0.687[b]
	4.95	0.631
	6.03	0.686
	6.26	0.650
	6.74	0.724
	7.14	0.766
	7.51	0.828

Table XIX (Cont'd)

Compound	pH	k_1^{obsd} (s^{-1})
10e	1.00	107.6
	1.52	45.8
	2.00	16.8
	2.46	9.59
	2.95	5.74
	3.92	5.07
	4.86	4.90
	5.61	4.63
10f	0.00	154.1
	0.52	59.4
	1.00	20.4
	1.52	7.54
	2.00	3.87
	2.43	2.94
	2.93	2.32
	3.90	2.57
	4.81	2.63
	5.53	2.46

Table XIX (Cont'd)

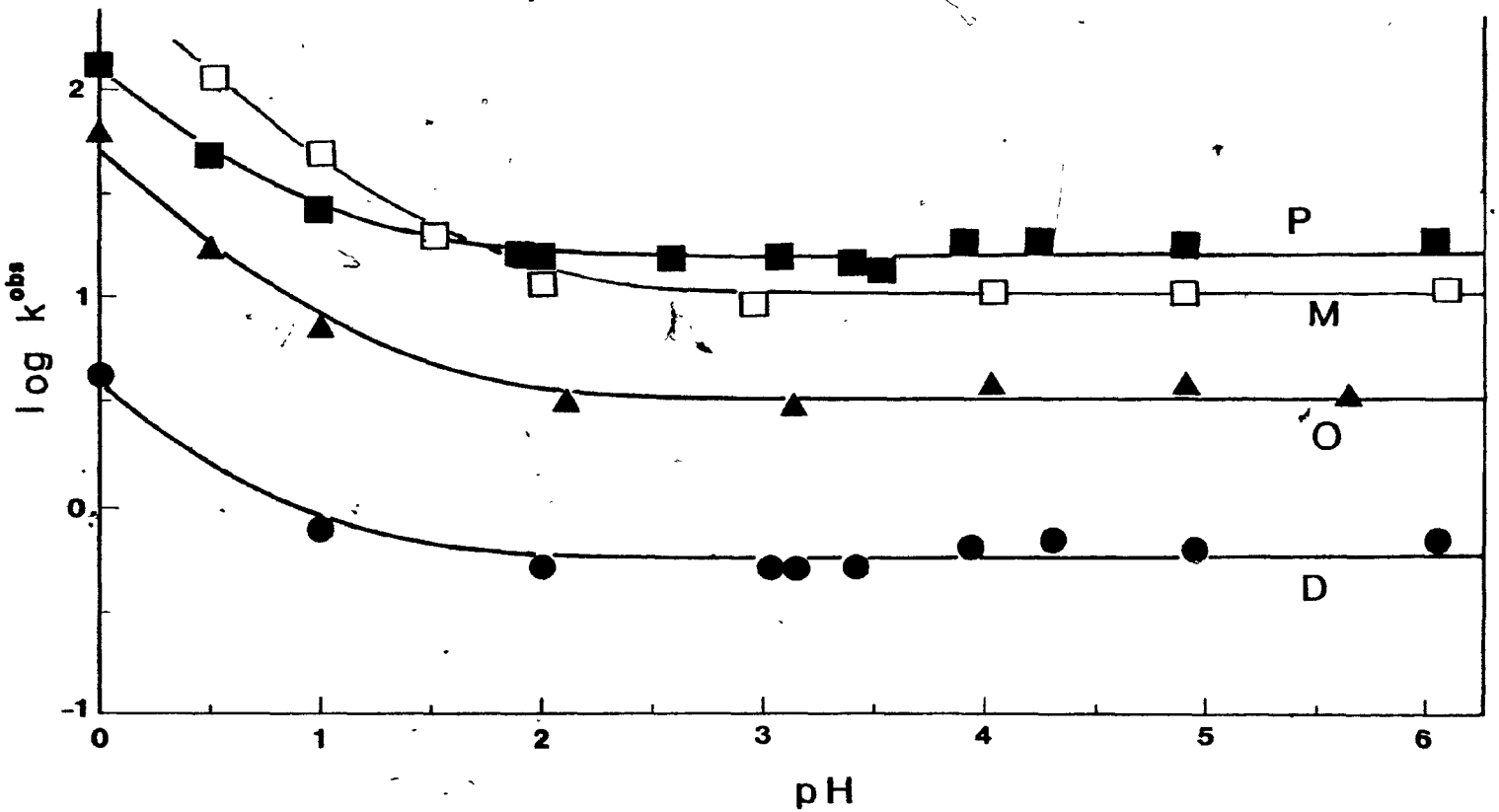
[a] At 25°C, in 0.1M KBr. At pH < 2 I= 0.1M KBr + (HCl)

[b] (Substrate) = 5×10^{-4}M; (Bromine) = 5×10^{-5}M.

[c] (Substrate) = 2×10^{-3}M; (Bromine) = 1×10^{-4}M.

[d] (Substrate) = 5×10^{-4}M; (Bromine) = 1×10^{-4}M.

Figure 12: pH-Rate profiles for the enolization of 4-bromo-2,5-cyclohexadienones 11a-11d. The profiles of 11e and 11f cross over the other rate profiles, therefore have been omitted for clarity.



o-product.

With phenol (10a) and the other substituted phenols 10b-10f the values of first-order rate constants (k^{obsd}) vary with pH as Shown in Figure 12 and in Table XIX. The acidity dependance for the decay of 11 can be expressed by equation 60

$$k^{obsd} = k_H \{H^+\} + k_0 \qquad (60)$$

where k_0 represents a spontaneous or "water-catalyzed" reaction of the intermediate 11 and k_H the catalytic constant for proton catalysed enolization of 11.

(B) Buffer Catalysis:

Acetone undergoes enolization by general base and by specific acid-general base catalysis.[28] By analogy with such simple ketones the enolization of 4-bromo-2,5-cyclohexadienones (11) would be expected to show similar buffer catalysis. It was observed that the dienone of 2,6-dimethylphenol (11d) did show, as expected, catalysis by carboxylic acids / carboxylate buffers. As mentioned earlier 2,6-dimethylphenol dienone (11d) was chosen for extensive studies in the present work as it was formed more rapidly and decomposed more slowly than others.

Table XX

Rate Constants for the Buffer Catalysis of the Enolization of the Dienone 11d.

Acetate Buffer

Buffer Strength (M) // pH:	4.20	4.69	4.99
0.01	0.594	0.608	0.610
0.05	1.26	1.28	1.29
0.1	2.05	2.14	2.16

Chloroacetate Buffer

Buffer Strength (M) // pH:	2.57	3.03	3.42
0.01	0.454	0.462	0.426
0.05	0.620	0.605	0.549
0.1	0.813	0.773	0.695

Succinate Buffer

Buffer Strength (M) // pH:	4.98	5.48	6.01
0.01	0.559	0.549	0.564
0.05	1.20	1.13	1.08
0.1	2.00	1.85	1.75

Table XX (Cont'd)

3-Chloropropionate

Buffer Strength (M) // pH:	3.51	3.97	4.51
0.01	0.456	0.486	0.478
0.05	0.607[b]	0.720[b]	0.825[b]
0.1	0.793[b]	1.04[b]	1.25[b]

Cyanoacetate[d]

Buffer Strength (M) // pH:	1.76	2.12	2.42
0.025	0.506	0.493	0.487
0.05	0.564	0.531	0.519
0.075	0.604	0.571	0.553
0.1	0.637	0.605	0.590

Methoxyacetate

Buffer Strength (M) // pH:	3.14	3.42	3.76
0.01	0.529	0.540	0.540
0.025	0.623	0.633	0.639
0.05	0.787	0.789	0.792
0.075	0.953	0.961	0.960
0.1	1.11	1.11	1.12

Table XX (Cont'd)

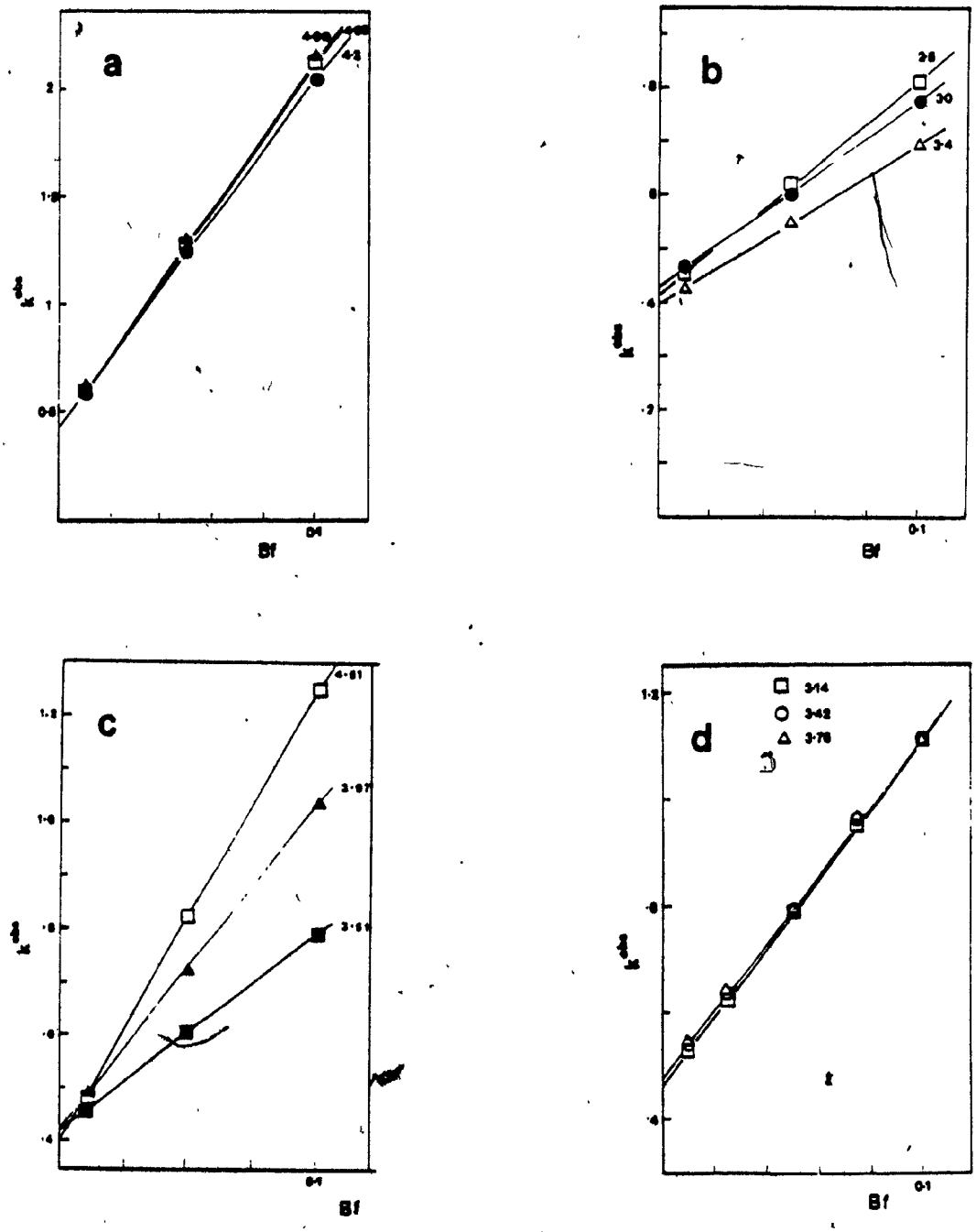
[a] At 25 °C, total ionic strength = 1M (NaCl). Unless otherwise noted (S) = 5×10^{-4}M and (Br_2) = 1×10^{-4}M.

[b] (S) = 5×10^{-4}M and (Br_2) = 2×10^{-4}M.

[c] (S) = 5×10^{-4}M and (Br_2) = 3×10^{-4}M.

[d] Only substrate in buffer, bromine in 1M NaCl.

Figure 13: Buffer plots. (a) For acetate buffer. (b) For chloroacetate buffer. (c) For 3-chloropropionate buffer. (d) For methoxyacetate buffer. (At pH's indicated and units of Bf M and k^{obs} s^{-1})



Buffer catalysis studies were done in acetate, cyanoacetate, 3-chloropropionate, methoxyacetate, chloroacetate and succinate buffers. Individual buffer plots are found to be strictly linear and the observed rate constants with the different buffer systems are given in Table XX and the individual buffer plots are shown in Figures 13a-13d (except for succinate and cyanoacetate). The data can be represented by equation 61

$$k^{obsd} = k_0 + k_t (B)_t \qquad (61)$$

where k_0 represents the enolization of 11 in the absence of buffer and k_t is the weighted sum of the buffer catalysed processes, as discussed below (equation 64). The slopes of individual buffer plots (k^{obsd} vs (B_t)) correspond to k_t values and the intercepts to k_0 values. Analysis of these slopes (Table XXI) in terms of the fractions of carboxylate anion (A^-) and the carboxylic acid (HA) (Figure 14) give the catalytic constants k_A and k_{HA}. This approach derives from the following:

$$k_t (B)_t = k_A (A^-) + k_{HA} (HA) \qquad (62)$$

Thus

$$k_t = k_A \frac{(A^-)}{(B)_t} + k_{HA} \frac{(HA)}{(B)_t} \qquad (63)$$

Table XXI

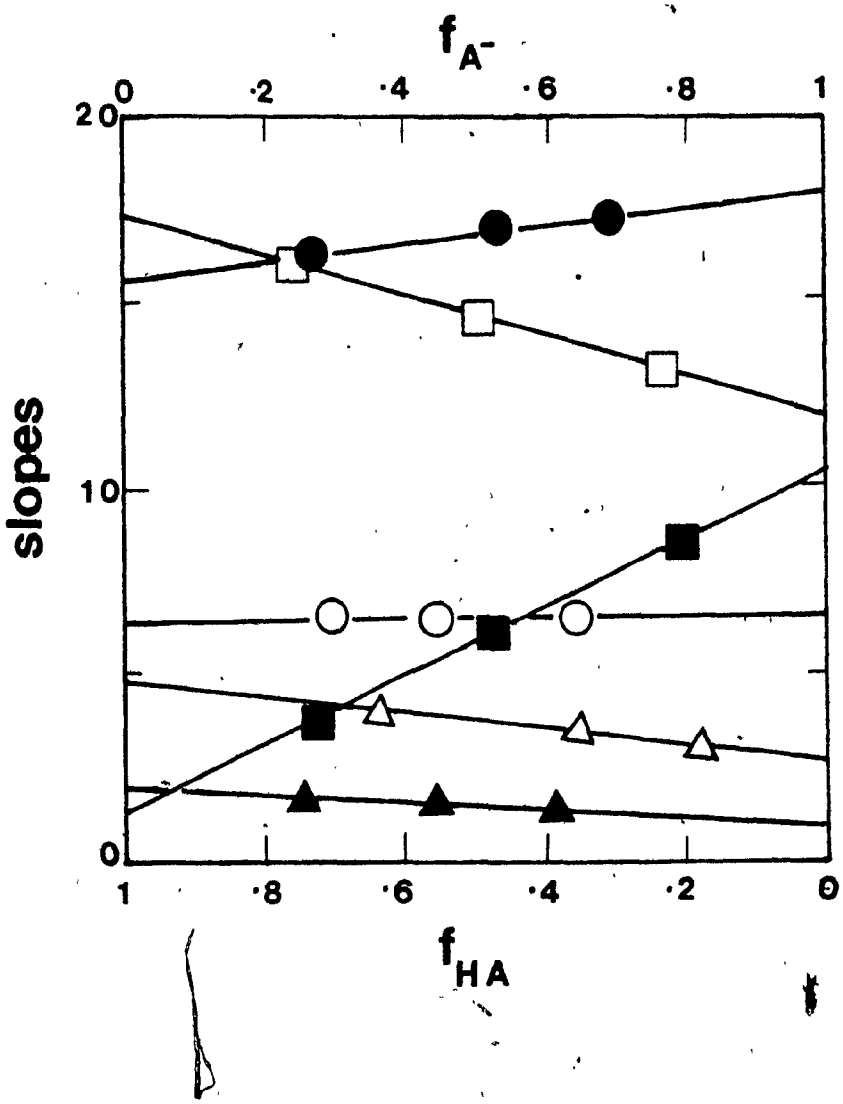
Results Obtained From Buffer Plots for 2,6-Dimethylphenol.

Buffer	pH	f_{A^-} [a]	Slopes [b]
Acetate	4.20	0.262	16.2
	4.69	0.529	17.0
	4.99	0.691	17.3
Chloroacetate	2.57	0.365	3.98
	3.03	0.645	3.45
	3.42	0.821	2.99
Succinate	4.98	0.244	16.0
	5.48	0.506	14.5
	6.01	0.764	13.2
3-Chloro-propionate	3.51	0.275	3.74
	3.97	0.523	6.17
	4.51	0.792	8.57
Cyanoacetate	1.76	0.253	1.73
	2.12	0.437	1.5
	2.42	0.608	1.37
Methoxyacetate	3.14	0.295	6.49
	3.42	0.443	6.39
	3.76	0.635	6.44

[a] $f_{A^-} + f_{HA} = 1$.

[b] Units: $M^{-1} s^{-1}$.

Figure 14: Slopes from buffer plots Vs fraction of buffer acid (f_{HA}) and buffer anion (f_{A^-}).



Acetate (●), succinate (□), 3-chloropropionate (■), methoxyacetate (○), chloroacetate (△) and cyanoacetate (▲).

$$k_t = k_A f_{A^-} + k_{HA} f_{HA} \qquad (64)$$

where f_{A^-} and f_{HA} are the fraction of anion of acid and fraction of the acid, respectively. From the k_A and k_{HA} values obtained for each buffer (Table XXII) it is clear that the enolization of 11 to 12 is, in fact, catalyzed both by general acids and by general bases as observed with the enolization of simple ketones.[28]

The slope of the plot of log k_A against pK_a of a series of catalysts gives the measure of the sensitivity of of the reaction to the strength of the basic catalyst. Such a plot corresponds to the Bronsted equation[70] for general base catalysis:

$$\log k_A = \log G_B + \beta (pK_a) \qquad (65)$$

where G_B is the constant for a particular reaction. The plot of log k_A against pK_a with the observed data (Figure 15 lower part) gives a slope of 0.54 which is the Bronsted β for the general base catalysis of the enolization of 11d.

A distinct feature to note in the Table XXII is that the values of k_{HA} vary very little for acids spanning seven pK_a units (-1.74 to 5.45). Logarithmic plots of the catalytic constants k_{HA} against pK_a (upper plot of Figure 15) gives a slope of 0.05 (S.D. 0.08) which is designated as

Table XXII

Catalytic Rate Constants for the Enolization of the Cyclohexadienone (11d) Derived from 2,6-Dimethylphenol (10d).

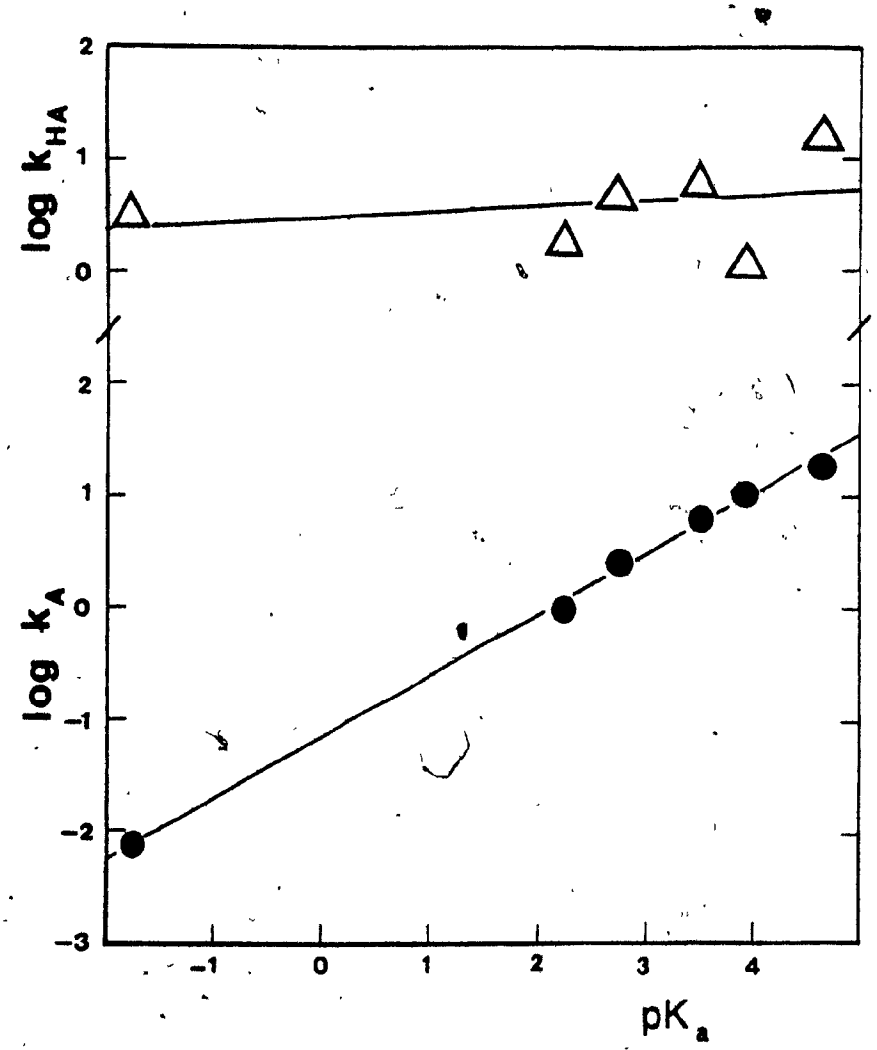
Acid (HA)	pK_a [a]	k_A ($M^{-1}s^{-1}$)	k_{HA} ($M^{-1}s^{-1}$)
Hydronium ion	-1.74	0.00766 [b]	3.17
Cyanoacetic	2.33	0.956	1.97
Chloroacetic	2.74	2.64	6.78
Methoxyacetic	3.52	6.37	6.50
3-Chloro-propionic	3.93	10.5	1.21
Acetic	4.65	18.2	15.6
Succinate monoanion [c]	5.49	11.9	17.2

a. The pK_a values are averages obtained from various papers of Jencks. (Ref: 73 and 74)

b. This value equals $k_0/55.5$, where k_0 is the average intercept of the buffer plots, 0.425 s^{-1}.

c. Omitted from the Bronsted plots because the succinate monoanion may act as both an acid and/or a base.

Figure 15: Bronsted plots for the general acid catalysis (upper part)- and general base catalysis (lower part) of the enolization of 11d to 12d.



Brönsted α and is the measure of the sensitivity of the reaction to the acid strength of general acid catalysts. This can be expressed by the Bronsted equation for general acid catalysis:[70]

$$\log k_{HA} = \log G_A - \alpha (pK_a) \qquad (66)$$

where G_A refers to the reaction constant. The α value of 0.05 is essentially equal to zero for a genuine general acid catalysis or a $\beta = 1.0$ (because $\beta = 1-\alpha$) for specific acid / general base catalysis. This low value of α is quite unusual for the enolization of a ketone.[75]

Discussion

From the pH-rate profiles (Figure 12) it is clear that in all these cases the mode of decay of the intermediates is same, and that equation 60 is applicable for all the substrates 10a-10f. The corresponding k_H and k_0 values for the dienones 11a-11f are given in Table XXIII. From the previous studies it has been established that the ease of formation of the dienone increases with increasing steric hindrance of phenolic hydroxyl which means the deprotonation should be slower accordingly. If the k_0 and k_H values of 10a, 10b and 10d are compared there is a decrease in the

Table XXIII

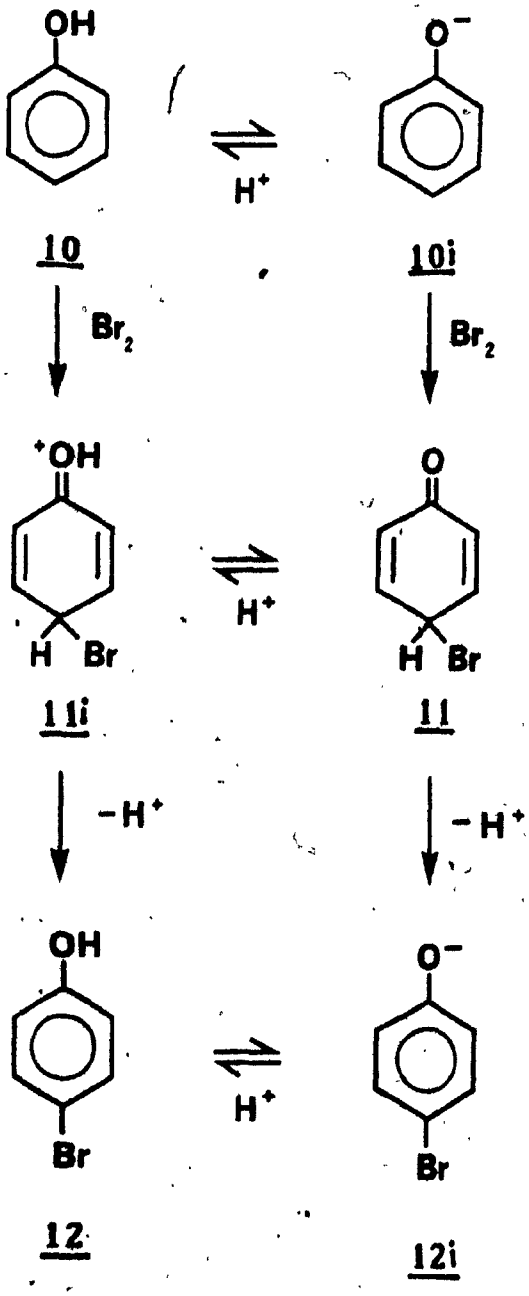
Rate Constants for the Enolization of Cyclohexadienones (11) formed during the Bromination of Phenol (10a), o-Cresol (10b), m-Cresol (10c), 2,6-Dimethylphenol (10d), 3,5-Dimethylphenol (10e) and 2,5-Dimethylphenol (10f).[a]

Phenol	k_H ($M^{-1}s^{-1}$)	k_O ($M^{-1}s^{-1}$)	pK_a of 10^{32}
10a	111	16.1	9.95
10b	48.2	3.22	10.28
10c	36.1	9.98	10.08
10d	3.17	0.572[b]	10.63
10e	11.90	4.81	10.19
10f	169	2.41	10.41

[a] At 25 °C, ionic strength = 0.1M KBr, with (buffer) = 0.01M except for pH < 1.

[b] The average value obtained from the intercepts of buffer plots (I = 1.0M) is 0.425 s^{-1}.

Scheme 14



k_O and k_H values as the steric hindrance of the phenolic hydroxyl increases from phenol to 2,6-dimethylphenol. Overall the results can be expressed by the mechanism in Scheme 14.

At lower pH's a small amount of the protonated form of 4-bromo-2,5-cyclohexadienone (11i) is formed from which water abstracts the proton to form the product p-bromophenol (12). At higher pH the proton from the dienone intermediate (11) is simply abstracted by water to form the anion of the product 12i which gets protonated later to form the product 12.

Table XXIV

Solvent isotope effect data

Dienone	pH (pD)	k_{H_2O} / k_{D_2O}
11a	3.6	1.6
11d	4.3	2.0
11d	0.0	1.2

The enolization process, that is conversion of the cyclohexadienone intermediate (11) to the product p-bromo-

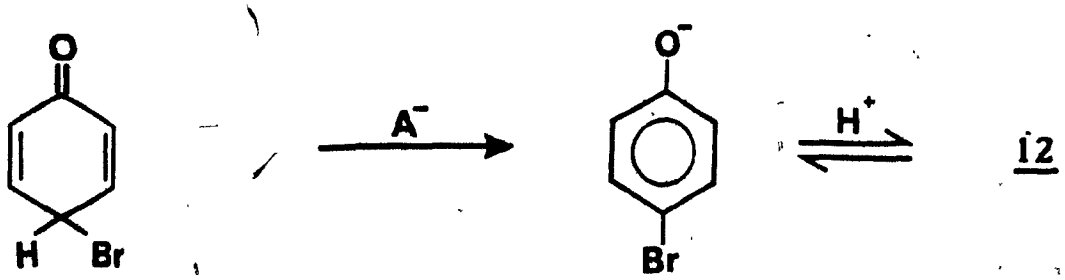
phenol (12), occurs by acid catalyzed and by water catalyzed pathways. The point that water acts as the base in the k_0 (deprotonation) process is confirmed by the solvent isotopic studies (Table XXIV). At pH (pD) 3.6 for phenol (10a) the observed solvent isotope effect is 1.6 and for 2,6-dimethylphenol at pH (pD) 4.3 it is 2.0. For the K_H process, if a specific acid / general base catalysis (where water acts as the base) is involved, then a value of less than 1.0 should be observed for k_{H_2O} / k_{D_2O}. But for the dienone of 10d at pH (pD) = 0 the observed k_{H_2O} / k_{D_2O} is 1.2 indicating that the catalysis is not simple specific acid / general base as observed in enolization of simple ketones.[28]

Evidence that both k_0 and k_H correspond to rate-limiting deprotonation of 11 was obtained by primary isotopic effect studies. With perdeuterophenol as the substrate the rates for the decay of the corresponding dienone were measured. The k_H / k_D at pH (pD) = 4.4 is 7.8 and at pH (pD) = 0 it was observed to be 3.8. At pH (pD) = 0 the k_H (H^+) term is dominant and at pH (pD) = 4.4 the k_0 term is more significant. These k_H / k_D values imply that both k_0 and k_H are associated with C-H bond cleavage.

The k_H / k_D values are consistent with the data

obtained by de la Mare and his co-workers for the dienone formed from 2,6-di-t-butylphenol in acetic acid.[14] In the present work a primary kinetic isotopic effect of 3.8 is observed for 11a in aqueous acid whereas the isotopic effect reported by de la Mare is 4.2 in acetic acid, 3.8 in aqueous acetic acid (water upto 3M)[15] and 2.2 - 3.3 in acetic acid containing perchloric acid and varying amounts of LiBr.[16] At pH (pD) = 4.4 the value observed in the present study is 7.8 and this is within the range reported by de la Mare and coworkers for acetic acid containing sodium acetate and water (0 - 2.6 M) as 6.7 - 8.8.[18] Grovenstein et al[76] have reported a value of 6.2 for the aqueous iodination of phenol with high concentrations of added iodide under which conditions enolization of the iododienone is rate-limiting.

From the buffer catalysis studies, the observed value of the Bronsted exponent β for the general base catalysis is 0.54. This, together with the primary kinetic isotopic effect of 7.8 (at pH (pD) = 4.4) is consistent with the general base abstracting the proton from 11 to form the anion of the product 12i (equation 67) in the rate-limiting step.

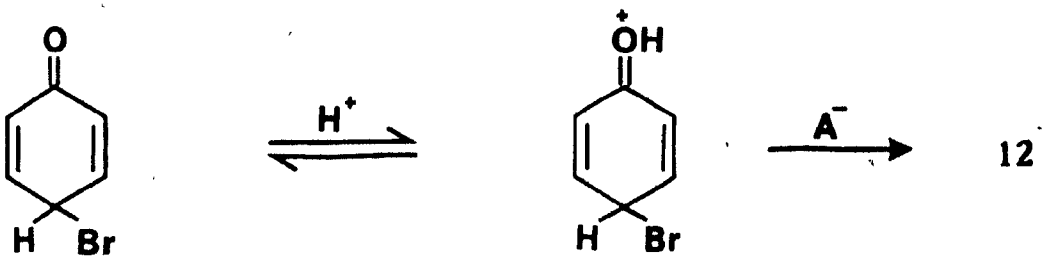


11 12l 12 (67)

From the β value and the isotope effect it seems that the C_4 proton is approximately half-transferred to the base A^- at the transition state (Bronsted coefficients may be interpreted as a measure of the proton transfer in the transition state. This interpretation is only roughly correct since a variety of factors can affect the stability of the transition state).[71]

For general acid catalysis the results indicate α to be $\simeq 0$ for a genuine general acid catalysis or a $\beta \simeq 1.0$ for a specific acid / general base type of catalysis. These values are unusual and cannot be explained by simple enolization mechanisms.

Various 4,4-dimethyl-2,5-cyclohexadienones have protonation pk's of -1 to -2.5.[77,78] Therefore, it is estimated that the 4-bromodienones 11i have pK's of less than -3.



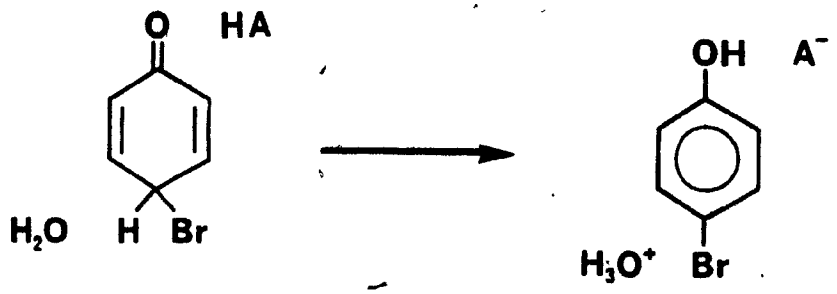
11 11i

(68)

Thus, a simple rate-limiting proton transfer from general acids (pK_a -1.74 to 5.45) to 11 would be energetically unfavourable and should give a Bronsted $\alpha > 0.5$[28] and not $\alpha \simeq 0$ as observed. On the other hand, if the reaction is visualized as involving a specific acid / general base catalysis as shown in equation 68, the value of β for the deprotonation of 11i to 12 should be less than 0.5 for the following reasons. The deprotonation 11i to form 12 is

energetically favourable and compared to the proton transfer from 11 to form the anion of the product 12i (where β = 0.54) the proton transfer from 11i to 12 should be easier and should give a lower β value. It can be noted that in case of anisole it has been reported[79] that for C-protonation the α is 0.71 which means the β for the reverse reaction, which is similar to 11i ⟶ 12 is 0.29. In contrast the β value observed in the present case is 1.0. The solvent isotope effect of 1.2 observed for 11d at pH 0 (Table XXIV) is also not consistent with the mechanism proposed in equation 68.

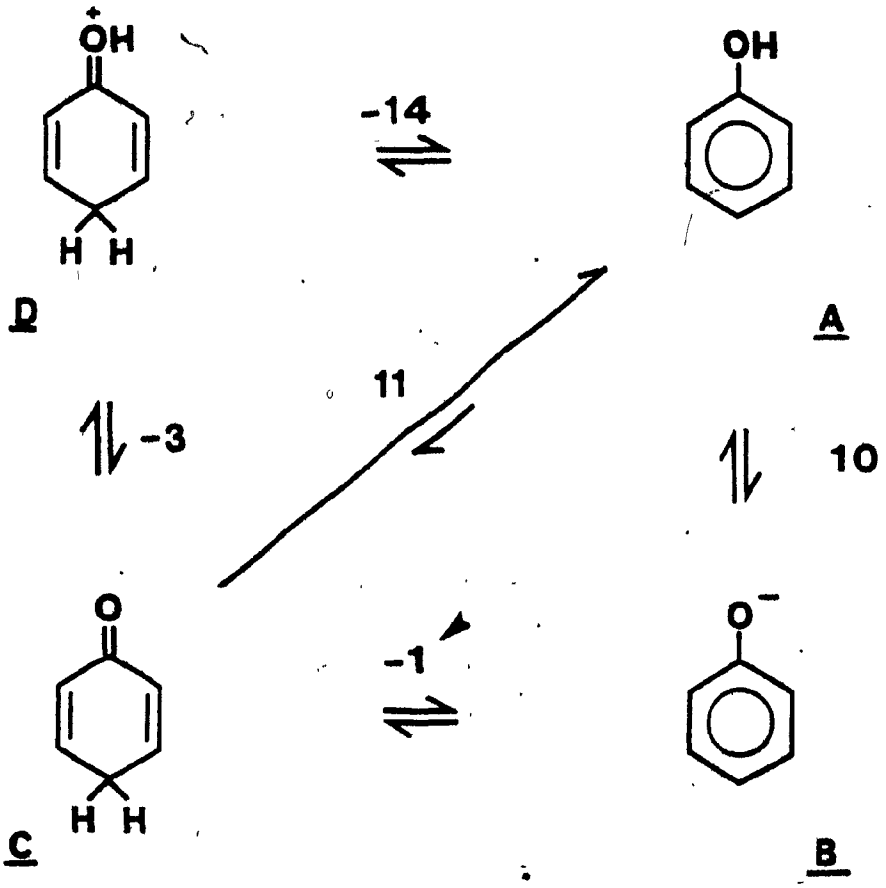
The general acid catalysis on the other hand can be explained by a termolecular mechanism as shown in equation 69:



11 12 (69)

Scheme 15: The tautomerization of phenol.

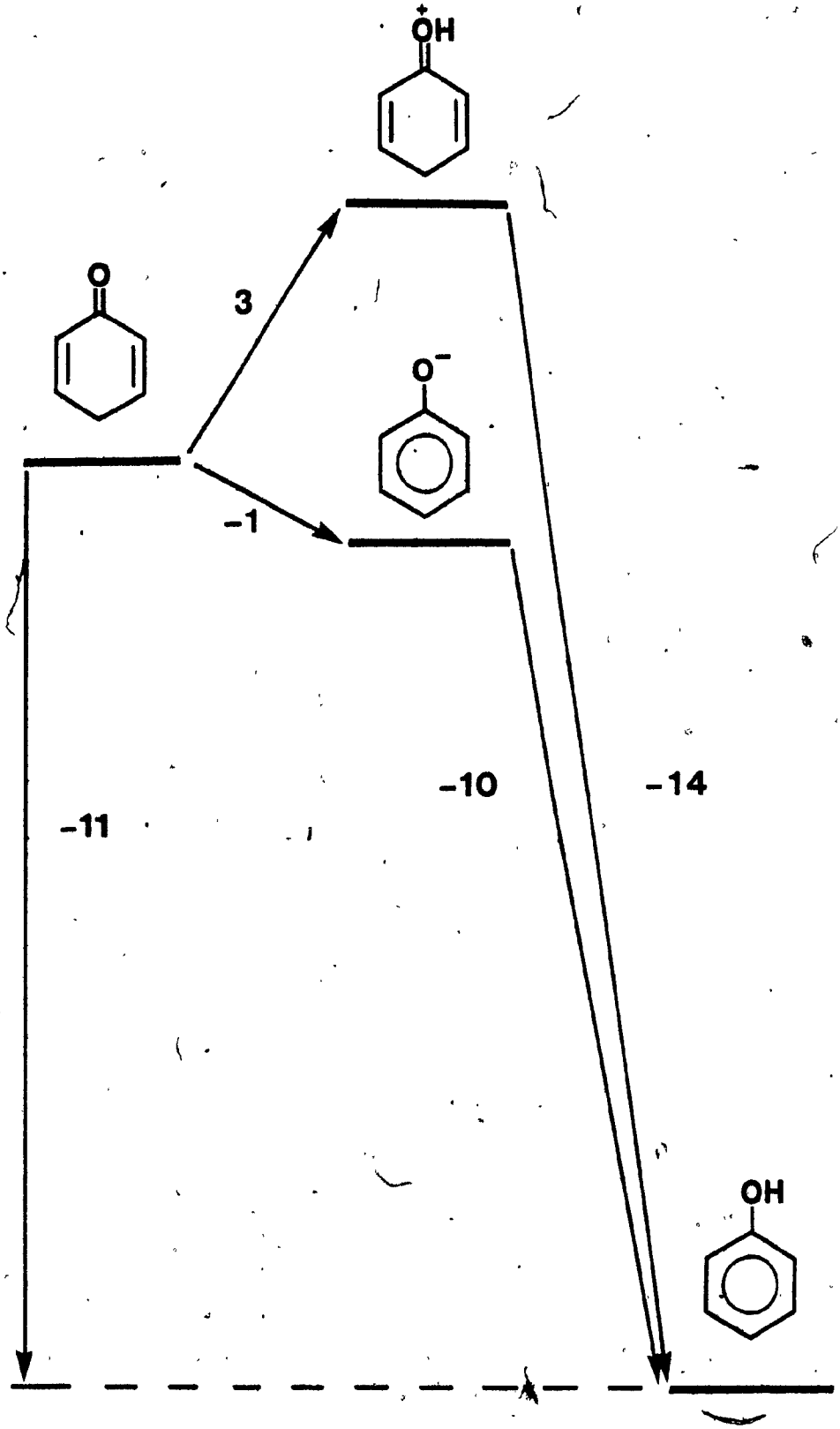
(These numbers represent actual or estimated pK values).



In this case, water abstracts the C_4 proton of 11 and the general acid, HA protonates the incipient phenoxide ion. This is analogous to the nucleophilic addition to carbonyl compounds which also exhibit general acid catalysis The sensitivity to the strength of the catalyzing acid α increases steadily as the nucleophilic strength of the attacking reagent decreases,[70] i.e. for weak nucleophiles α approaches to one and for strong nucleophiles it decreases to zero.

This unusual enolization mechanism in phenols can be explained by the energetics of the tautomerism of phenol (Scheme 15). Phenol (A) and the cyclohexadienone (C) are tautomers. The pK for the protonation of C_4 of phenol has been estimated to be -14.[80] For the protonation of the oxygen of the cyclohexadienone tautomer (C) it is -3. (This is because for the protonation of 4,4-dimethyl-2,5-cyclohexadienone Cook and Waring have reported a value of -2.4[56] and in this case without the two geminal 4-methyl groups it should be slightly more negative). From this, the enol / keto ratio for phenol can be estimated to be 10^{11}. However, the pk_a of phenol is 10 which means that the cyclphexadienone tautomer (C) C_4 proton has a pK_a of -1! which is surprisingly low for a C-H acid.

Scheme 16



If this situation is represented in terms of relative free energies (Scheme 16) the reasoning will become clearer, Even in 1M HCl (pH 0) where each pK_a is directly proportional to the ΔG_0 for the individual step, the pathway from the cyclohexadienone (C) to phenol (A) via the phenoxide ion (B) is of lower energy and is thermodynamically preferred over the pathway which involves the formation of protonated cyclohexadienone cation (D). Now, in the present study, where bromination of phenol is concerned, the 4-bromo substituent in the intermediate cyclohexadienone (11) will stabilize the anion 12i and destabilize the protonated cyclohexadienone cation 11i and therefore the anionic pathway in Scheme 16 should be even more favoured. In particular the conversion of 11 to 12i should correspond to $pK_a \simeq -2$ (for phenol itself the estimated pK_a for conversion of C $\longrightarrow$ B is -1 (Scheme 15) and a p-bromo substituent lowers the pK_a of phenol by 0.6 units[32]). Therefore the deprotonation of 11a by water should have ΔG_0 near zero, which is consistent with the observed large primary kinetic isotope effect of 7.8 for the k_0 process (cf Results section).

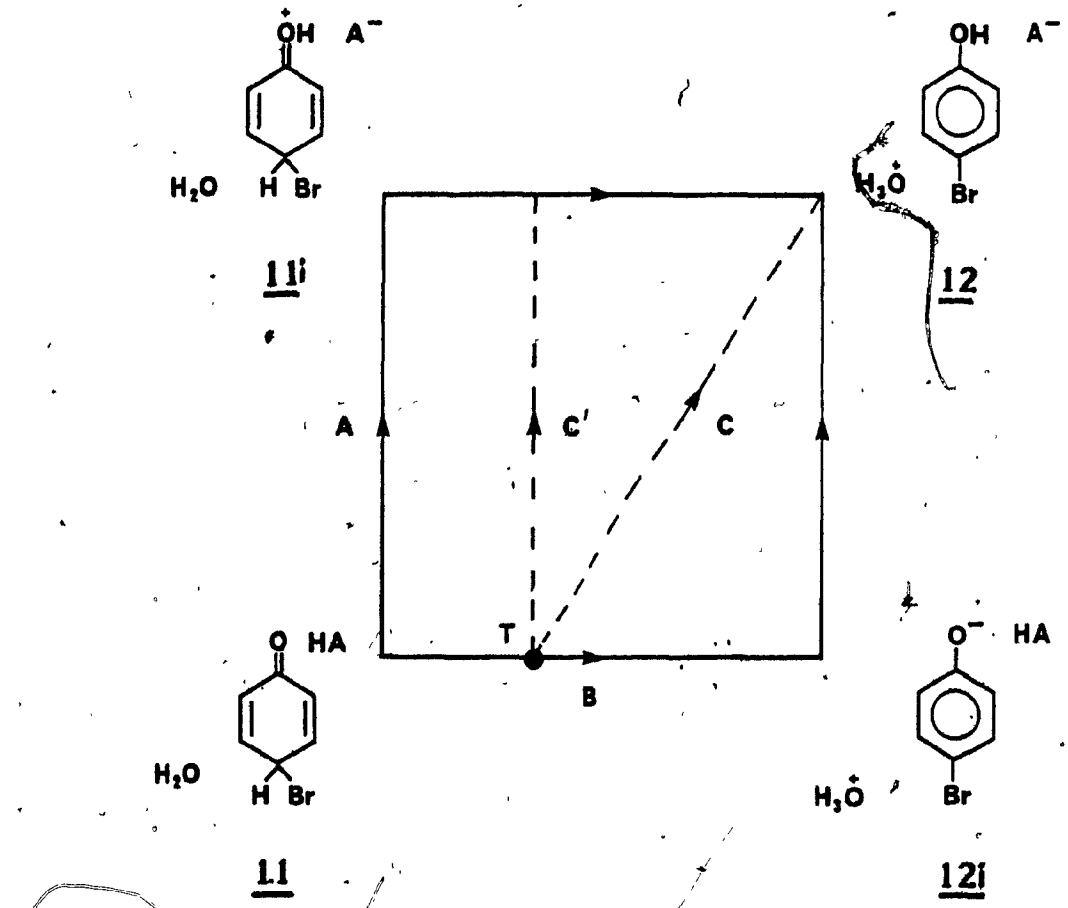
This enolization mechanism in dilute acid is very much different from that observed for enolization of simple

ketones.[28] In the case of acetone, the enolization process is energetically uphill since the enol / keto ratio is about 10^{-8}.[81] The pK for enolate formation is 19[81-83] whereas that for protonation of acetone is about -5.[84] Thus, in acidic solution, the protonated form of acetone is a viable intermediate on the route to the enol whereas the enolate is not.[85]

The general acid catalyzed enolization mechanism for the dienones 11 which is shown in equation 69 can be better explained by using a free-energy reaction-coordinate diagram (Figure 16). Following the arguments given above for the tautomerization of phenol, pathway B via the anion (12i) should be energetically more favourable (< by 5.5 kcal mol^{-1}) compared to pathway A via the protonated dienone (11i). Pathway A is ruled out by the data on the basis that any degree of proton transfer to the carbonyl oxygen of the dienone (11) would make the proton abstraction by water or other general bases easier and should result in a β value < 0.5, the value observed for general base catalysis. In contrast, the observed data require $\beta \sim 1.0$.

The observed data are more consistent with the pathway labelled C (Figure 16) and a transition state T with

Figure 16: Free energy reaction-coordinate surface for the general acid catalyzed enolization of 11 ⟶ 12.



with some anionic character. The location of T is based on $\alpha \sim 0$ (insignificant H-A bond rupture) and the primary kinetic isotope effect of 3.8 (C_4-H bond $\sim$ 30% ruptured). The acid catalyst HA may contribute to the stabilization of the incipient phenoxide ion by hydrogen-bonding in the transition state[86] but may transfer its proton only after sufficient negative charge has formed on the oxygen as to make the proton transfer favourable.[87,88]

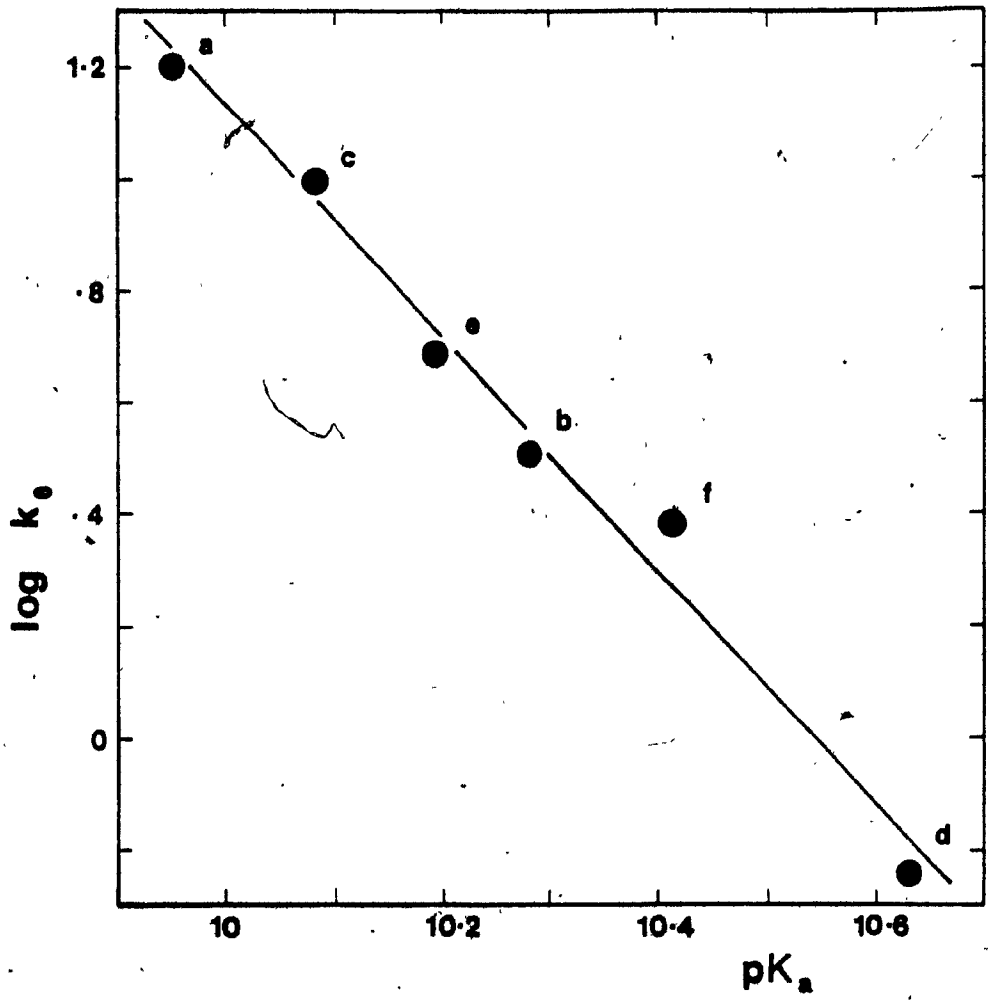
A variant of pathway C which is possible is C', as kindly suggested to us by Prof. J.P. Guthrie (Figure 16). At a point on the pathway B, when there is enough charge formed on the oxygen, the proton is transferred from the general acid HA which is hydrogen-bonded to the oxygen, causing a switch to pathway A, thus avoiding the energy maxima of both pathways A and B. This is similar to various pathways proposed by Guthrie[87] for reactions of carbonyl compounds which are catalysed by general acids and bases. The proton transfer from HA which is hydrogen-bonded to dienone 11 to the developing negatively charged oxygen has little or no energy barrier, therefore the sensitivity to the general acid catalyst (HA) will be very small ($\alpha \sim 0$) unless the pK_a of HA is greater than 9 (the pK_a of the product p-bromophenol 12).[87] Pathway C or C' essentially

corresponds to a preassociation mechanism of the type proposed by Jencks.[86] The 4-bromophenoxide ion (12i) at lower pH's may not exist for any appreciable time as proton transfer within the encounter complex (12i.HA) may be faster than diffusional separation of the two species.[86,89] Thus the HA must be present, most probably hydrogen-bonded to 11, before the C_4 proton is abstracted to form 12i.

The effect of substituents on enolization via the general base catalyzed route can be considered by correlating the rates of enolization with the stability of the product 4-bromophenoxide ions (12i). Unfortunately the pK_a's of all the substituted 4-bromophenols are not available and so the pK_a's of the starting phenols 10a-10f were used, assuming the effect of a 4-bromo substituent to be relatively constant. A plot of log k_0 Vs pK_a of these substrates (Figure 17) shows a good correlation (r=0.9919) and gives a slope of -2.09 (S.D. 0.13) and intercept 22.01 (S.D. 1.37). From the magnitude of the slope it is evident that the rate of proton abstraction is quite sensitive to the pK_a of the starting material and presumably to that of the product also. From Figure 17 it can be seen that for more acidic phenols (containing electron-withdrawing groups) the k_0 will be much higher and so, in retrospect, it is not

Figure 17

Plot of k_o (the rate constant for the water catalysed enolization of 11a-11f) Vs the pK_a's of the parent phenols.



surprising that we were not able to detect dienones formed from such phenols.

With k_H values (Table XXIII) there seems to be no obvious correlation. This may be due to the different effects of the methyls at 2(6)-and 3(5)- positions on the two proton transfers shown in equation 69. The methyl groups at any position should retard proton abstraction from C_4 (cf Figure 17). Methyl groups at 2- and 6- positions should have a negative steric effect on the proton transfer to oxygen and a positive effect when the methyl groups are at 3- and 5- positions.

In case of salicylic acid (5) the dienone was not observed. This may be due to the presence of the electron-withdrawing substituent $-CO_2H$ which should increase the value of k_0, as discussed above. Alternatively, the $-CO_2H$ group in the dienone may function as an internal general acid catalyst and so facilitate the enolization process.

Summary:

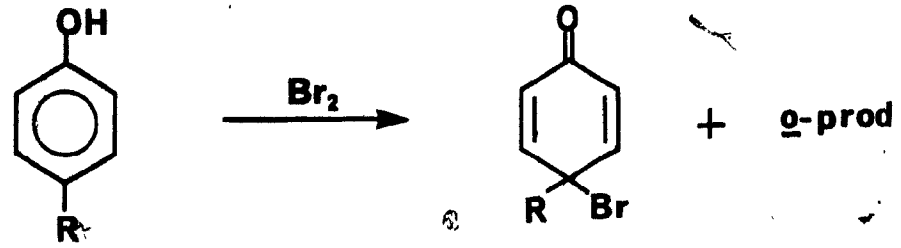
Transient cyclohexadienone intermediates have been observed in the bromination of phenol and several methylated phenols in aqueous solution. The enolization of these intermediate dienones to p-bromophenols is catalyzed

by acid and by water in the pH range studied (0-6). Furthermore, from buffer catalysis studies it is evident that the enolization reaction can be catalyzed by general bases (β = 0.54) and by general acids ($\alpha \simeq 0$). The β value of 0.54 is explained by simple rate-limiting proton abstraction from the C_4 of the 4-bromo-2,5-cyclohexadienone (11) (equation 67). The very low α value cannot be explained by specific acid/general base catalysis, as is the case with simple ketones.[28] The low α value is attributed to a termolecular transition state (water, 4-bromo-2,5-cyclohexadienone (11) and general acid (HA)) in which there is proton abstraction (C_4 proton of 11) by water and a proton transfer from the hydrogen-bonded general acid HA when there is sufficient negative charge developed on the oxygen of the dienone (pathway C or C' in Figure 16).

CHAPTER 5

The Formation Of Ipso-Dienones.

Phenols generally show greater reactivity for bromine attack at para positions than at ortho.[9,10] For example, phenol undergoes ~ 82% para attack[10] and o-bromophenol is ~4times more reactive than p-bromophenol.[10] These observations led us to consider a study of the bromination of p-alkyl phenols, where some of the initial attack of bromine might occur ipso to the para alkyl substituent (15 ⟶ 16).



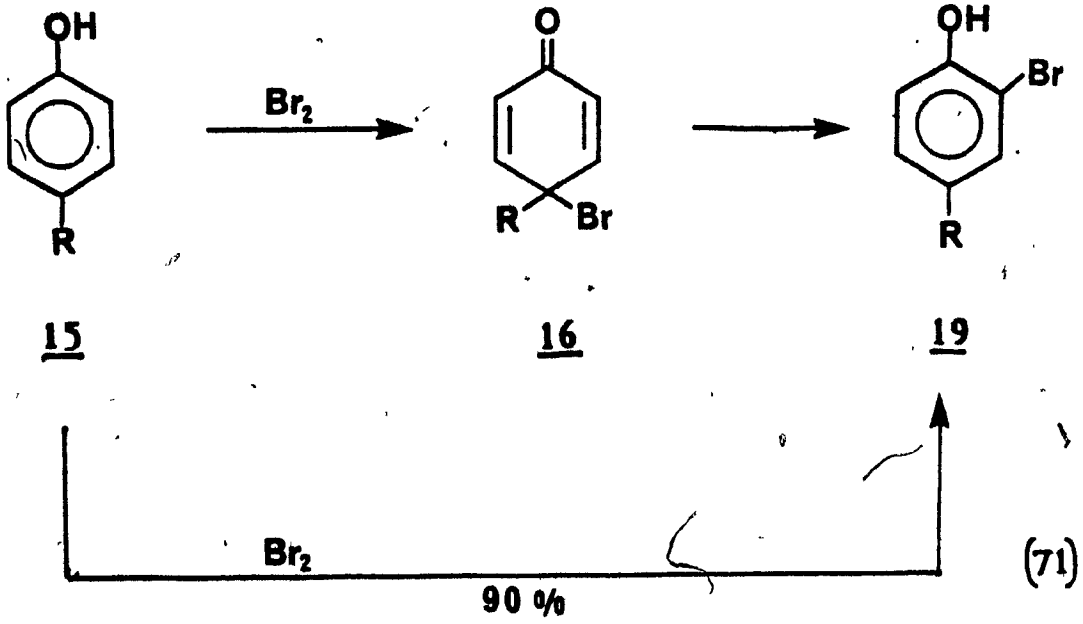
15 16 (70)

Recent work in the literature suggested that such a study was feasible. Fischer et al isolated (in part)

" ipso-dienones " from the reaction of chlorine[108] and bromine[22] with p-alkyl phenols (15) in non aqueous solvents. Earlier, Baciocchi and Illuminati had studied the formation of analogous dienones from the reaction of bromine with 4-R-2,6-di-t-butylphenol in acetic acid.[19] From their studies it seemed that the nature of 4-alkyl group does not greatly influence the rate of formation of the ipso-dienone. However, when the 4-substituent was a polar group (Br) the rate was considerably retarded (and not measured). In the present study it was observed that the rate of debromination of the ipso-bromo dienones also is not greatly affected by the nature of the 4-alkyl group.

In aqueous bromination of 4-alkyl phenols ipso-dienones (16) were observed at $\sim$ 250 nm with an absorbance about 1/10 of that found for the cyclohexadienones (11) dicussed earlier. This is probably due to the initial formation of $\sim$ 90% of the major product o-bromophenol (19) and about 10% of the ipso-dienone (16). Subsequently, 16 is converted to o-product. The overall reaction can be presented as in equation 71.

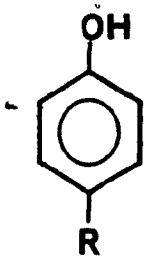
Intramolecular reactions are generally faster than the corresponding intermolecular process. Therefore, an attempt was made to generate ipso-dienones with an ortho-



carboxyl group to observe if this group affected their debromination. It was found that with the ipso-dienone of 5-methylsalicylic acid (8b) there is considerable rate increase for the debromination step, compared to that of p-cresol (16a).

Results:

The ipso-dienones formed in the bromination of 4-alkyl phenols can be considered to represent a dead end. As is shown later, they decompose by debromination back to the



R	
(a)	Me
(b)	t-Bu

15

4-alkyl phenols which then undergo bromination to form the o-bromo product. The decomposition of the ipso-dienones was studied in detail with p-cresol (15a) and p-t-butyl phenol (15b) as the substrates. Several others have been studied in this laboratory.[42] It was observed that the decomposition of the 4-alkyl-4-bromo-2,5-cyclohexadienones (16) (ipso-dienones) is independent of substrate and bromine concentrations but is linearly dependent on bromide ion concentrations and on the H^+ concentration. This can be seen in Figure 18 (a and b) in which the variation of the rate of the decomposition of the 4-methyl-4-bromo-2,5-cyclohexadienone (16a) in 0.1M KBr and 1M KBr with pH is shown. With p-t-butyl phenol it was observed that pH rate-profile was superimposable with that of p-cresol, therefore it is plotted separately in Figure 18c. The first-order rate constants for the decomposition of these ipso-dienones are given in Table XXV. Together with the results for other p-

Table XXV

Rate Constants for Debromination of the Ipso-Dienones Formed by the bromination of p-Cresol (15a) and p-t-butylphenol (15b).[c]

Compound	pH	k_1^{obsd} (s^{-1})
15a[a]	0.00	1.01[d]
	1.00	0.089
	1.52	0.030[d]
	2.00	0.012[d]
15a[b]	0.00	5.74
	0.50	2.56
	1.00	0.817
	1.50	0.259
	2.00	0.084
	2.32	0.035
	2.88	0.012
15b[a]	0.00	1.075[d]
	1.00	0.093[d]
	2.00	0.011[d]
	2.38	0.0044[d]
	2.87	0.0016[d]

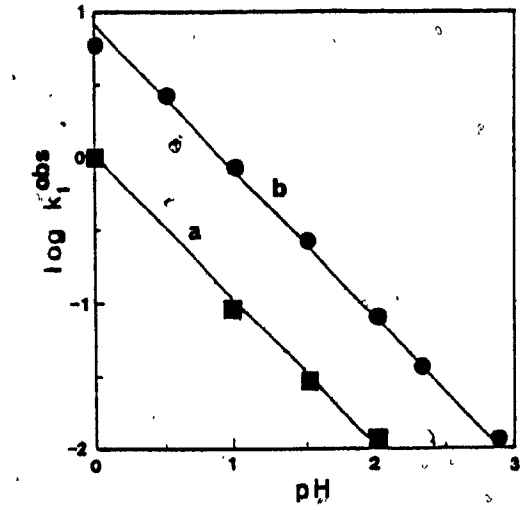
a. Carried out in 0.1 M KBr. b. Carried out in 1M KBr.

c. (S) = 5×10^{-4} M, $(Br_2) = 5\times10^{-5}$ M.

d. (S) = 5×10^{-4} M, $(Br_2) = 10^{-4}$ M.

Figure 18

Decomposition of the Ipso-Dienones of (a) p-Cresol (15a) in 0.1M KBr; (b) p-Cresol (15a) in 1M KBr; (c) p-t-Butylphenol (15b) in 0.1M KBr.



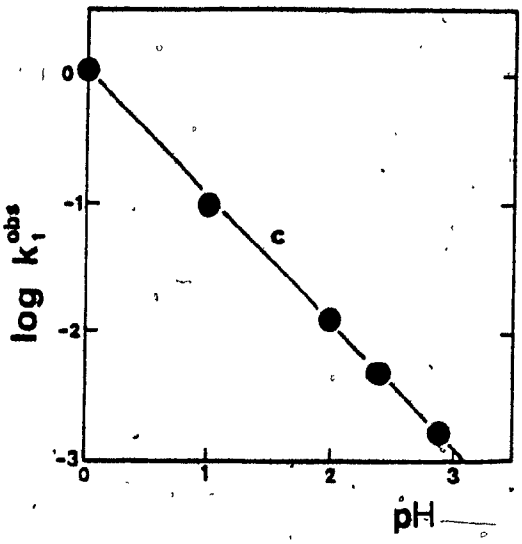


Table XXVI

First-Order Rate Constants for the Decomposition of the Ipso-Dienones (16) obtained from various 4-Alkyl Phenols (at pH 0, in 0.1M aqueous KBr).

R	k^{obsd} / s^{-1}	Ref.
Me	1.02	(i)
Et	0.624	42
Pr	1.29	42
i-Pr	0.755	42
t-Bu	1.08	(i)
3.4-DiMe	2.00	42

(i) Present study.

alkyl phenols[42] they indicate that the effect of the size of the 4-alkyl group on the debromination is almost insignificant (see Table XXVI).

From Figure 18 (a-c) it is clear that the decomposition of the ipso-dienone (16) varies linearly with the acidity and this can be expressed by equation 72:

$$k^{obsd} = k\,(H^+) \qquad (72)$$

where k is the rate constant for acid-catalyzed debromination at fixed (Br^-).

The study of ipso-dienones was extended to 5-methylsalicylic acid (8iv) to observe the effect (if any) of the ortho carboxy in debrominaton. As mentioned earlier in Chapter 3, the dienone from 5-methylsalicylic acid (8b) was indeed observed and from the pH-rate profile (Figure 7) it is evident that the debromination of this dienone is faster than that of the ipso-dienone from p-cresol (15a). To be more precise, at around pH 2 the factor is about 225. As discussed in Chapter 3 this can be attributed to the effect of ortho-carboxy group which functions as an intramolecular general acid catalyst. The data for the debromination of the ipso-dienone 8b are given in Table XVIII (Chapter 3).

Since the enolization of the 4-bromo-2,5-cyclo-

Table XXVII

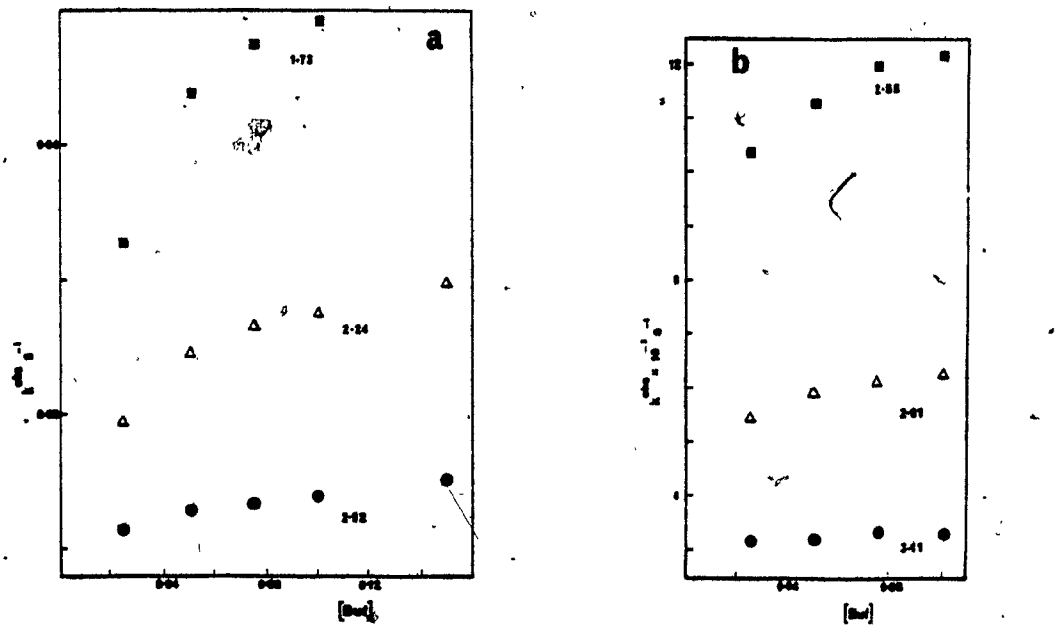
Rate Constants for the Buffer Catalysis of the Debromination of 4-Methyl-4-Bromo-2,5-Cyclohexadienones.[a]

Buffer strength (M) // pH	1.73	2.24	2.52
Cyanoacetate Buffer			
0.025	0.0328	0.0195	0.0115
0.05	0.0439	0.0246	0.0129
0.075	0.0475	0.0266	0.0134
0.1	0.0492	0.0276	0.0140
0.15	-	0.0299	0.0153
Chloroacetate Buffer			
0.025	0.0104	0.00547	0.00316
0.05	0.0113	0.00594	0.00321
0.075	0.0120	0.00616	0.00335
0.1	0.0122	0.00631	0.00335

a. $(S) = 5\times10^{-4}$ M, $(Br_2) = 5\times10^{-5}$ M, at 25 °C, in 0.5M KBr, total ionic strength 1M (made up with NaCl).

Figure 19

Buffer Plots for the Debromination of the Ipso-Dienones of p-Cresol: (a) Cyanoacetate Buffer; (b) Chloroacetate Buffer



hexadienones (11) was found to be general acid-catalyzed (Chapter 4) it was anticipated that the debromination of the ipso-dienones 16 would show similar catalysis. Therefore buffer catalysis studies were carried out to calculate the Bronsted α values for this acid-catalyzed reaction. Studies with cyanoacetate and chloroacetate buffers gave buffer plots that were distinctly curved. The data relating to these two studies are given in Table XXVII and the curved plots are shown in Figure 19 (a and b).

Buffer catalysis studies were also done in the presence of trapping reagents. In these experiments the ipso-dienone was first generated and then immediately mixed in the stopped-flow instrument with the trapping agent (phenol) so that the bromine released in the debromination reaction reacts immediately with the excess of the trapping agent. With this set of buffer studies the plots obtained were mostly linear at lower buffer concentrations but at higher buffer concentrations slight curvatures were still observed. The buffer catalysis data for the trapping experiments are given in Table XXVIII and the plots in Figure 20 (for experimental details regarding the trapping experiments refer to Chapter 7).

Table XXVIII

Rate Constants for the Buffer Catalysis of the Debromination of 4-Methyl-4-Bromo-2,5-Cyclohexadienones by Trapping the liberated free Bromine with Phenol.[a]

Buffer strngth (M) // pH[b]	1.61	1.85	1.98	2.18
	Cyanoacetate Buffer			
0.025	0.0621	0.0375	0.0301	0.0161
0.05	0.0805	0.0468	0.0378	0.0216
0.075	0.0976	0.0548	0.0430	0.0257
0.1	0.1110	0.0611	0.0471	0.0298
0.15	0.126	0.0691	0.0526	0.0314

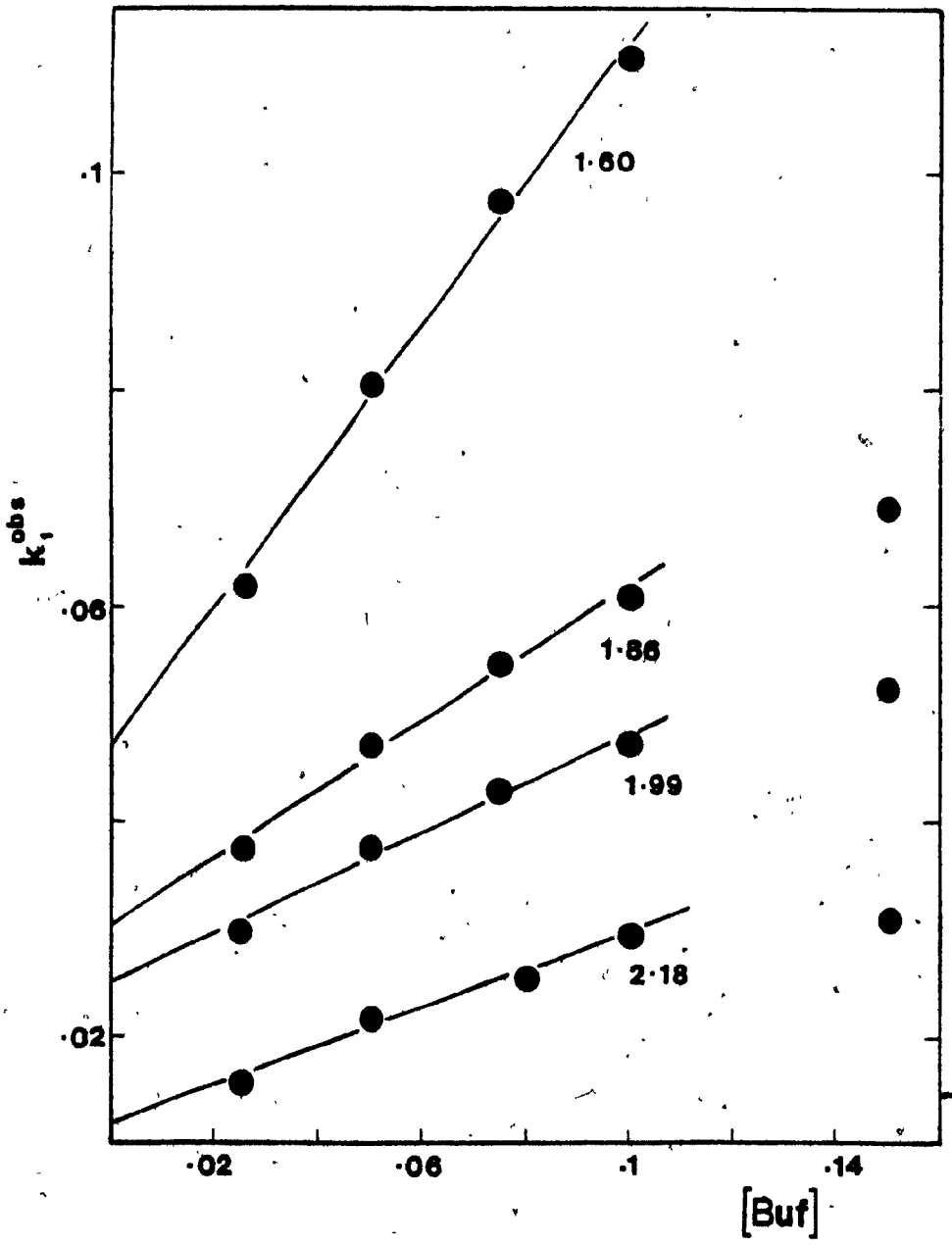
a. A mixture of p-cresol 8×10^{-4} M and bromine 8×10^{-4} M in 10^{-3} M sodium acetate was prepared and this mixture was immediately mixed in the stopped-flow apparatus with phenol 8×10^{-4} M in buffer of total ionic strength 2M (buffer strength + 1M KBr + remaining NaCl).

b. Final buffer strength and final measured pH.

Figure 20

Buffer Plots for the Debromination of 4-Methyl-4-Bromo-2,5-Cyclohexadienone by Trapping Experiments.

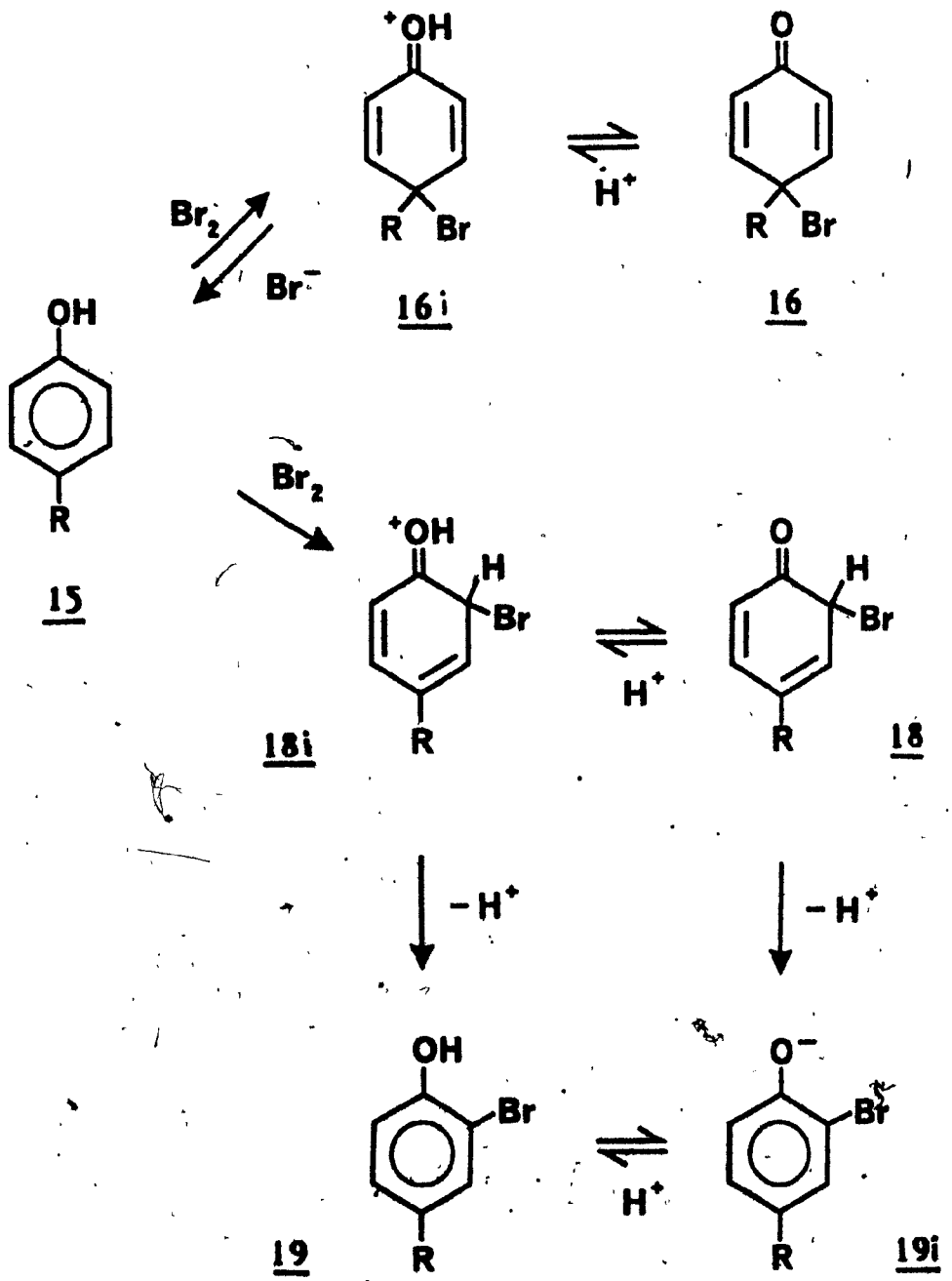
(cyanoacetate buffer)



Discussion:

The pH-rate data for the decay of the ipso-dienones (16) of p-alkyl phenols (15) can be rationalized by Scheme 17.

Scheme 17



First, the extent of absorbance change for the decomposition of 16 is only $\sim$ 1/10 that observed for the enolization of the dienones 11. This is attributed to $\sim$ 10% of the initial bromine attack on the p-alkyl phenols 15 leading to ipso-dienones 16, the remaining $\sim$ 90% attack being ortho. The o-dienones (18), which should be the major intermediate, could not be detected as they are very unstable[22,69] and undergo very fast enolization to the product, 19.

Second, the buildup and decay of the ipso-dienones (16) observed at 250 nm is consistent with the formation and decomposition of 4-alkyl-4-bromo-2,5-cyclohexadienones 16. These ipso-dienones are at a dead end as the migration of the bromo substituent to the meta position occurs only in very strongly acidic media.[22] From Figure 18 it is evident that these ipso-dienones undergo debromination by acid catalysis and that the rate is also bromide ion dependent. As is shown in Scheme 17 the ipso-dienone 16 reversibly forms 15 which then further gets brominated to give the major ortho product 19.

The rates of debromination (Table XXVI) of ipso-dienones with various alkyl groups indicate that the size of the alkyl group has very little effect. The absence of

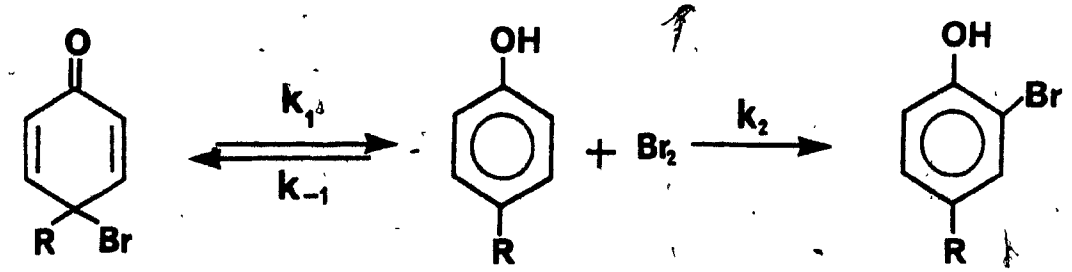
effect of the size of the alkyl group is similar to the results obtained by Baciocchi et al[19] for the rate of formation of related ipso-dienones in acetic acid.

Buffer catalysis studies were carried out to probe the nature of acid catalysis in the debromination step and trials with cyanoacetate and chloroacetate buffers resulted in curved buffer plots (Figure 19 a and b). These can be explained by Scheme 18 and the following equations. The first-order rate constants (k^{obsd}) can essentially be expressed as:

$$k^{obsd} = \frac{k_1 k_2}{(k_{-1} + k_2)} \qquad (73)$$

where k_1, k_{-1} and k_2 represent the rate constants for the debromination of the ipso-dienone, formation of the ipso-dienone (16) and bromination of p-alkyl phenols to form 19 respectively.

Scheme 18



16 15 19

The curvature in the buffer plots can be attributed to catalysis in two, possibly three, of the steps in Scheme 18: (i) general acid catalysis in the debromination of the ipso-dienones (16), (ii) general base catalysis for the formation of the ipso-dienone (16) and possibly (iii) general base catalysis in the bromination step leading to the formation of the o-bromo product (19).

If the debromination step 16 ⟷ 15 is general acid-catalyzed, then the reverse reaction 15 ⟶ 16 leading to the formation of the ipso-dienone must be general base-catalyzed, according to the Principle of Microscopic Reversibility. Furthermore, if the formation of the ipso-dienone is general base-catalyzed then the formation of o-dienones leading to the formation of o-product may also be general base catalyzed.

In this case equation 73 can be rewritten as

$$k^{obsd} = \frac{(k_1^0 + k_1^{HA}(HA))(k_2^0 + k_2^A(A^-))}{(k_{-1}^0 + k_{-1}^A(A^-) + k_2^0 + k_2^A(A^-))} \qquad (74)$$

Because

$$k_1 = k_1^0 + k_1^{HA}(HA)$$

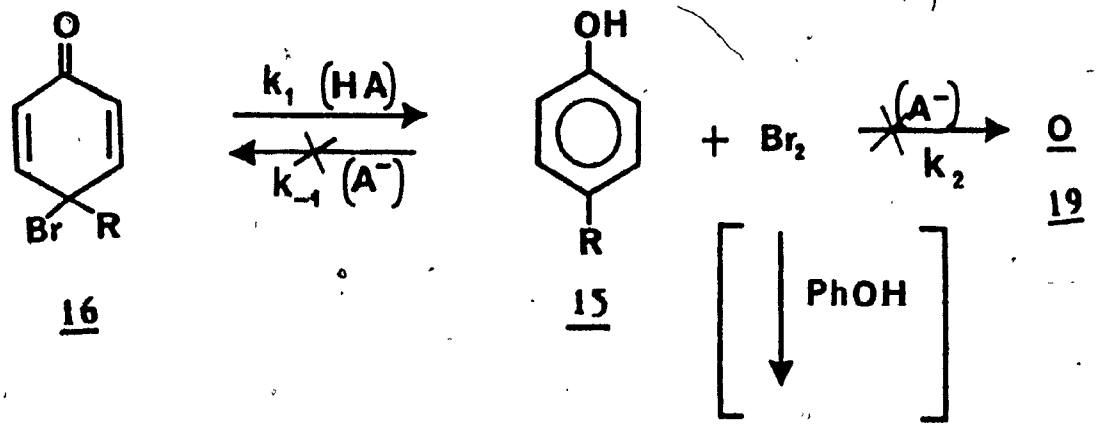
$$k_2 = k_2^0 + k_2^A(A^-)$$

$$k_{-1} = k_{-1}^{0} + k_{-1}^{A}(A^-)$$

where k_0 values refer to the rate constants in absence of buffer and the others to the respective buffer catalyzed steps. Analysis of curved buffer plots is very difficult, especially when the rate in the total absence of buffer is not available and the data do not show a well-defined plateau at high buffer concentration. Accordingly, a new set of experiments were designed in which the bromine liberated in the decomposition of the ipso-dienone was trapped so that the bromination steps (k_{-1} and k_2) were eliminated, leaving debromination (k_1) as rate limiting (Scheme 19). After some experimentation, an excess of phenol was selected as the trapping agent as the rate of bromination of phenol is similar to that of p-cresol. In these experiments a solution of the ipso-dienone 16 was generated (in 10^{-3}M sodium acetate) and then this solution was mixed with phenol in buffer in the stopped-flow apparatus.

Such trapping experiments gave buffer plots which were to a large extent straight, except at high buffer concentrations (> 0.1M) where there was slight curvature. Analysis of the slopes from the straight portions of buffer plots and plotting them against the f_{HA} (Figure 21) gives a

Scheme 19



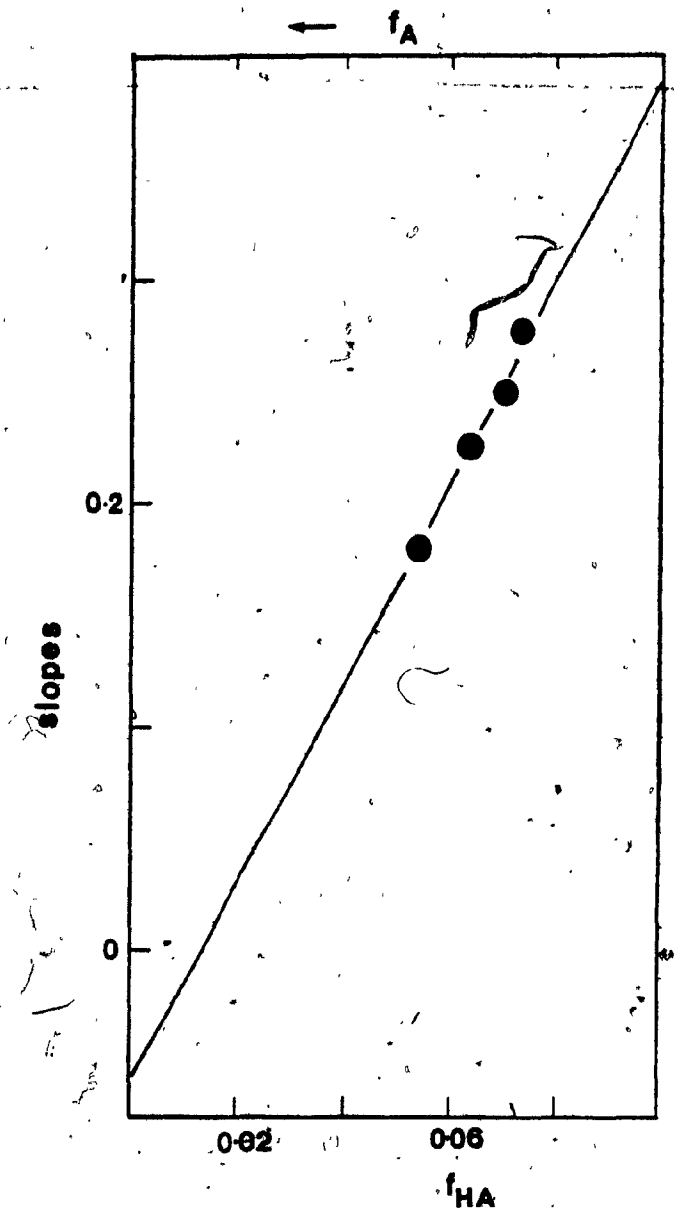
k_{HA} value of 0.392 and a k_A value of -0.061 (S.D. 0.032) for cyanoacetate buffer. This k_A value is almost equal to zero and the k_{HA} value of 0.392 clearly proves that the debromination of the ipso-dienones is buffer acid-catalyzed.

As explained earlier in Chapter 3, the bromination of 5-methylsalicylic acid (8iv) can be represented by Scheme 12 (Chapter 3). In this mechanism debromination of the ipso-dienone 8b occurs via the free acid form and the carboxyl group acts as an intramolecular general acid catalyst.

The efficiency of an intramolecularly catalyzed reaction can be measured if there are accurate rate measurements available for an intermolecular reaction of the same

Figure 21

Plot of Slopes Vs f_{HA} (data from the trapping experiments for the debromination of ipso-dienones).



type of mechanism. For the present case, p-cresol (15a) provides a suitable comparison since the debromination of its ipso-dienone (16) is catalyzed by external general acids. The ratio of the intramolecular rate to an appropriate intermolecular rate is referred to as the effective molarity (EM).[62] It is formally the concentration of the catalytic group (in this case an external acid) required to make the intermolecular reaction go at the observed rate of intramolecular process. To calculate a true EM a correction is needed to take account of the acidity of the carboxyl group which functions as the internal catalyst. The correction requires a linear free energy relationship between the acidity and the reactivity of general acids. For the general acid-catalyzed debromination of the ipso-dienone of p-cresol an approximate value for $\alpha \simeq 0.13$ can be estimated from the k_{HA} values of 0.4 $M^{-1}s^{-1}$ and 1.3 $M^{-1}s^{-1}$ for catalysis by cyanoacetic acid and hydronium ion, respectively. The expected rate constant for the intermolecular general acid-catalyzed debromination of 16 can be calculated from equation 75

$$\log k = \log k_0 - \alpha \Delta pK_a \quad (75)$$

where k_0 refers to the rate constant for the debromination

of 16 by hydronium ion and ΔpK_a is the pK_a differnce of 5-methylsalicylic acid (3.06) and hydronium ion (-1.74). Equation 75 is obtained by subtracting the Bronsted equation for H_3O^+ from the analogous equation for a general acid HA. The k calculated from equation 75 is 0.306 M^{-1} s^{-1} whereas the k_1 corresponding to the plateau constant obtained from the fitted data for 8b is 2.59 s^{-1} and therefore the EM = k_1 / k = 8.5M. This value is reasonably within the range of values cited for intramolecular general acid catalysis in Kirby's review.[62] Thus the intramolecular catalysis is more efficient than intermolecular catalysis and there is no competition with external acids, as indicated by absence of buffer catalysis for the debromination of the ipso-dienone 8b (Scheme 12, Chapter 3).

Summary:

Ipso-dienones (16) are formed as intermediates in the aqueous bromination of p-alkyl phenols (15). Bromine attack occurs ipso to an extent of ~ 10%, the remaining ~ 90% occurring ortho. The ipso-dienones decompose by debromination to reform the substrate which is then ortho brominated. This debromination reaction is general acid-

catalyzed and is bromide ion dependent (Figure 18). The size of the p-alkyl group has very little effect on the rate of debromination (Table XXVI). This is similar to the effect observed by Baciocchi and Illuminati[19] for the rate of formation of similar ipso-dienones in acetic acid.

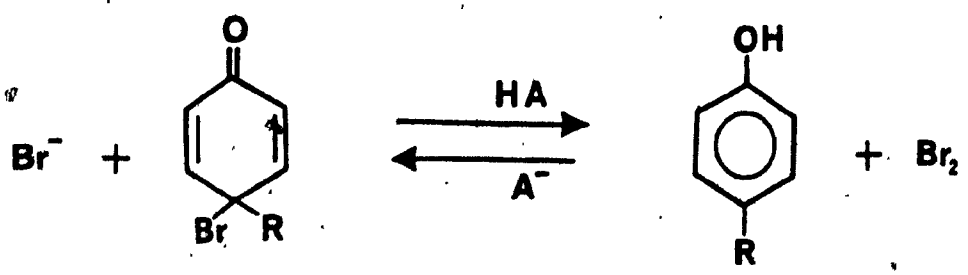
The linear buffer plots (Figure 20) observed when the bromine liberated in the debromination of the ipso-dienones is trapped by phenol indicate that the general acid-catalyzed debromination of the ipso-dienones (16) is predominant and the competing reactions i.e., bromination of p-alkyl phenols leading to the formation of o-product (19) and the ipso-dienones (16) are virtually eliminated. The k_{HA} value 0.39 and k_A value of $\simeq$ 0 indicate that the debromination is only catalyzed by general acids.

5-Methylsalicylic acid (8iv) also forms an ipso-dienone (8b) and its rate of debromination is much faster than that of the dienone derived from p-cresol. The enhancement in the rate can be attributed to intra-molecular general acid catalysis (Scheme 12, Chapter 3) of the debromination by the carboxyl group of 8b. The effective molarity (EM) for the internal catalytic group is estimated to be 8.5M.

CHAPTER 6

Buffer Catalysis Studies For The Bromination Of Phenol

In the previous Chapter it was established that the debromination of ipso-dienones is general acid-catalyzed. This implies, according to the Principle of Microscopic Reversibility, that the formation of the dienone should be general base-catalyzed.



16 15

(76)

If this is so, it is reasonable to suppose that normal bromine attack on phenols, is also catalyzed by general bases. Some initial studies were carried out with acetate and succinate buffers by Paventi, using phenol as substrate.[10] In these experiments it was observed that there was an increase in the rate of the disappearance of bromine

as the buffer concentration was increased. However, no definite conclusions were made as the pH of the buffers at different concentrations were not uniform. In the present study, buffer catalysis studies were carried out initially with p-bromophenol to confirm that the rate of formation of the dienone varies with buffer concentration and later, using phenol (10) as substrate, the studies were completed.

Results:

The disappearance of bromine was monitored at 275 nm for all these buffer catalysis studies to obviate interference from dienone enolization (Chapter 4). Preliminary studies were carried out with p-bromophenol and p-cresol as substrates but only at one pH for each type of buffer. With these substrates buffer catalysis was indeed observed and this led to further detailed studies using phenol as substrate. The buffers used were succinate, acetate and propionate. The second-order rate constants for these experiments are given in Table XXIX. The plots of the second order rate constants versus the buffer concentrations are all linear (Figure 22a - 22c) and can be explained by equation 77:

$$k^{obsd} = k_0 + k_t (B)_t \qquad (77)$$

Table XXIX

Second-Order Rate Constants for the Buffer Catalysis for the Attack of Bromine on Phenol (10).[a]

Buffer strength // pH (M)	3.75	3.99	4.18
Succinate Buffer[b]			
0.025	7.29×10^{5}	7.13×10^{5}	7.22×10^{5}
0.05	7.51×10^{5}	7.65×10^{5}	7.73×10^{5}
0.075	7.71×10^{5}	8.09×10^{5}	8.08×10^{5}
0.1	8.40×10^{5}	8.37×10^{5}	8.63×10^{5}

Buffer strength // pH (M)	4.26	4.86	5.36
Acetate Buffer			
0.025	5.68×10^{5}	6.94×10^{5}	1.08×10^{6}
0.05	5.74×10^{5}	7.16×10^{5}	1.15×10^{6}
0.075	6.16×10^{5}	7.78×10^{5}	1.22×10^{6}
0.1	6.52×10^{5}	8.14×10^{5}	1.27×10^{6}

Table XXIX (Cont'd)

Propionate Buffer

Buffer strength // pH (M)	4.28	4.53	5.06
0.01	5.12×10^{5}	5.42×10^{5}	7.70×10^{5}
0.025	5.36×10^{5}	5.82×10^{5}	7.92×10^{5}
0.05	5.78×10^{5}	6.26×10^{5}	8.96×10^{5}
0.075	6.30×10^{5}	7.06×10^{5}	---
0.1	6.94×10^{5}	7.56×10^{5}	1.01×10^{6}

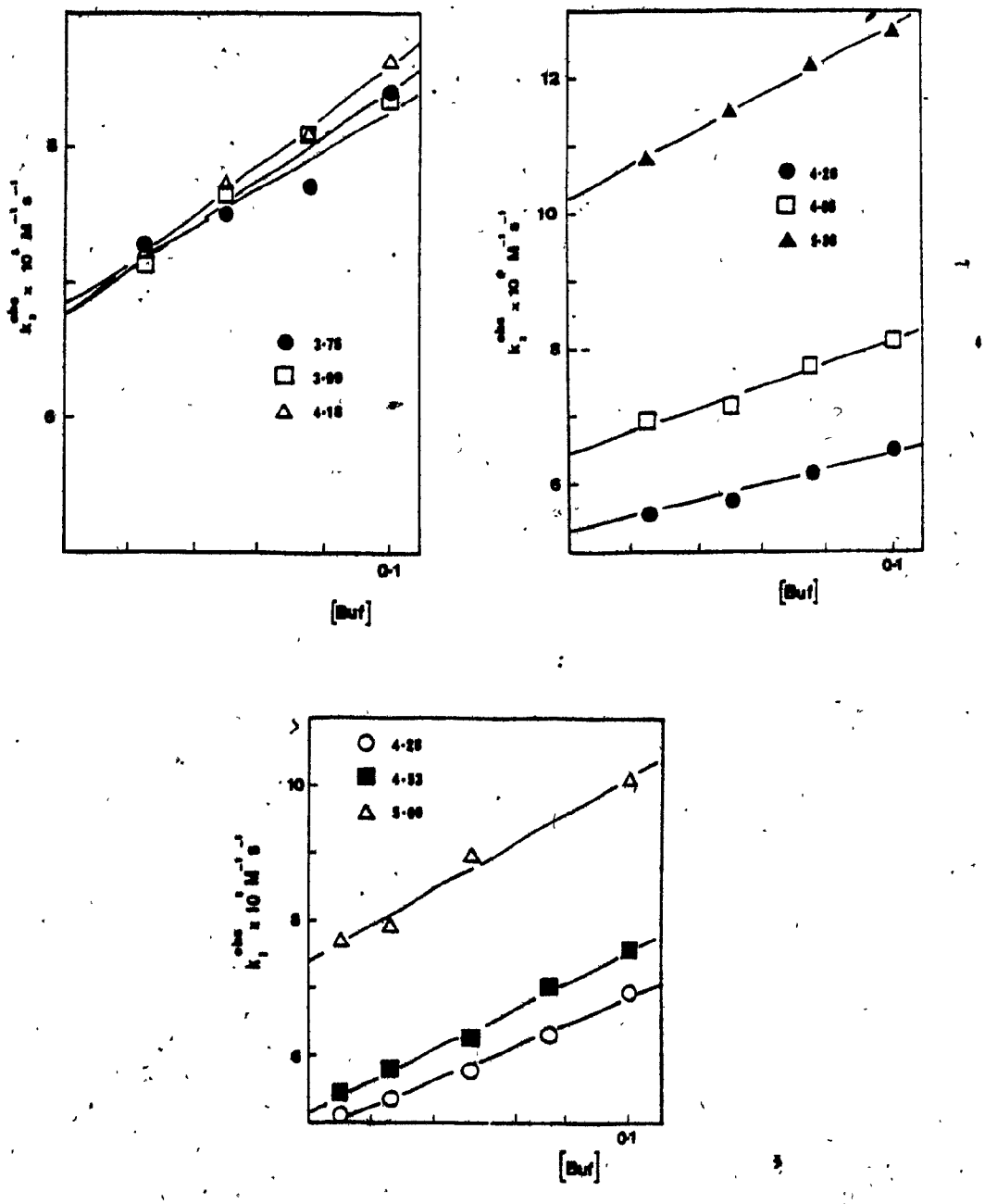
a. Units for rate constants M^{-1} s^{-1}, at 25 °C, total ionic strength 1M (buffer strength + 0.5M KBr + remaining NaCl) (S) = 5×10^{-4} M and (Br_2) = 5×10^{-5} M, values for second-order rate constants corrected for tribromide ion formation.

b. (S) = 10^{-4} M and (Br_2) = 10^{-5} M.

Figure 22

Buffer Plots for the Bromination of Phenol (a) Succinate,

(b) Acetate and (c) Propionate.



For each type of buffer an increase in the slope is observed with increase in pH and the intercepts also vary with pH (above 4.5).

Discussion:

From the slopes of the buffer plots it is evident that there is an increase in catalysis as the fraction of the basic component of the buffer increases. Further analysis of the slopes shows that general base catalysis is exhibited for the first step in bromination of phenol. Thus, as suggested above, the attack of bromine on phenol leading to the formation of the intermediate dienone is facilitated by general bases. Reasonable values of k_A were obtained from the plots of slopes versus the fraction of basic (acidic) component (Figure 23). The data also provide " k_{HA} values " which were not anticipated. In the case of acetate buffer the k_{HA} value obtained is 3.91×10^{5} (S.D. 4.16×10^{5}) $M^{-1} s^{-1}$, but, taking into consideration the standard deviation, this can be considered to be zero. With succinate and propionate buffers the k_{HA} values appear to be more significant. The k_A and k_{HA} values obtained from the plot of slopes against the fraction of the base (Figure 23) are listed in Table XXX.

Figure 23

Plot of Slopes versus f_{A^-}

(○) Succinate, (■) Acetate and (△) Propionate.

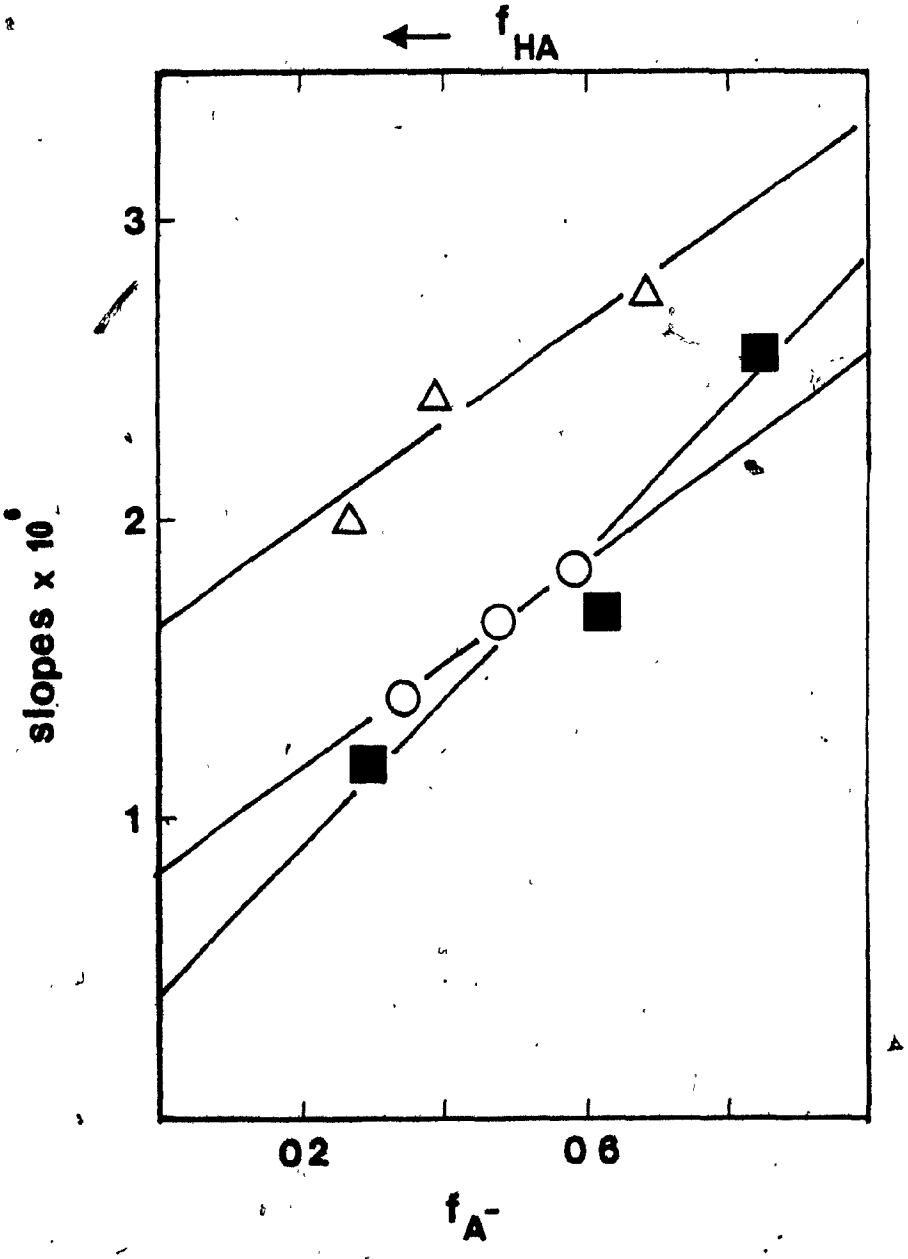


Table XXX

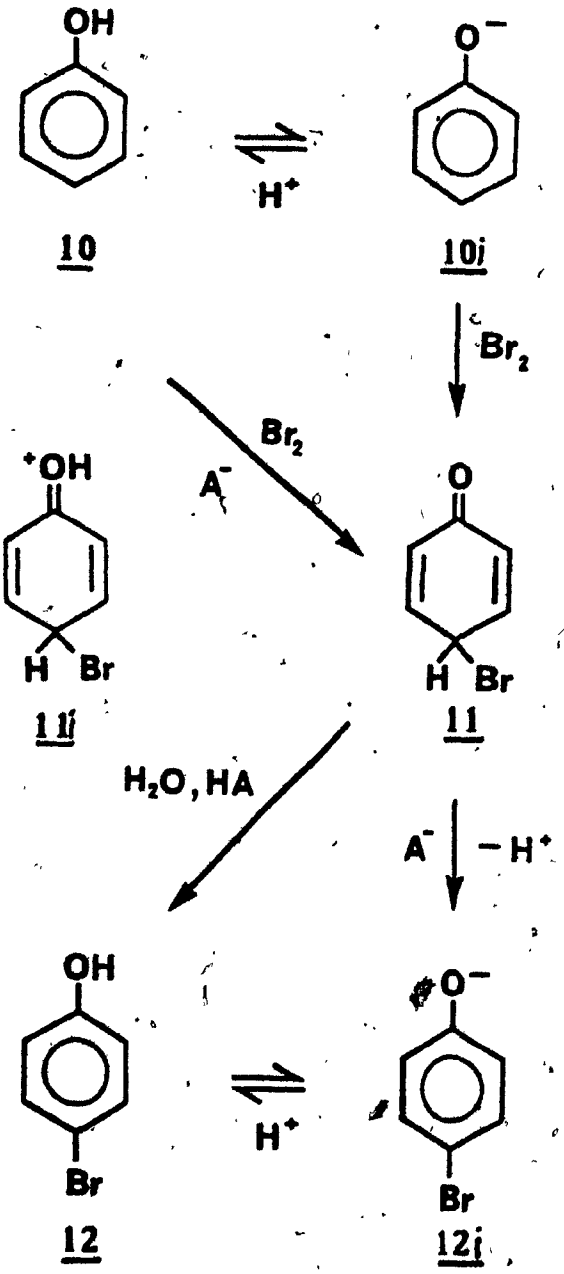
Catalytic Rate Constants for the Attack of Bromine on Phenol (10).

Acid (HA)	pK_a	k_A ($M^{-1}s^{-1}$)	k_{HA} ($M^{-1}s^{-1}$)
Succinic	4.04[a]	2.57×10^6	8.23×10^5 (S.D. 4.52×10^5)
Acetic	4.65[b]	2.83×10^6	3.91×10^5 (S.D. 4.16×10^5)
Propionic	4.73[a]	3.34×10^6	1.63×10^6 (S.D. 2.16×10^5)

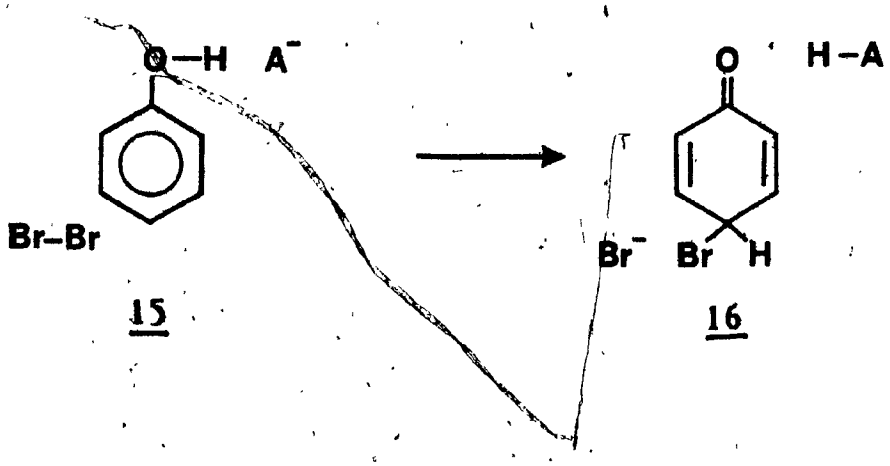
a. pK_a's from Ref. 32 corrected for 1M ionic strength.

b. Ref. 73.

Scheme 20


OH
O⁻
H⁺
10
10i
Br₂
Br₂
A⁻
⁺OH
O
H Br
H Br
11i
11
H₂O, HA
A⁻
−H⁺
OH
O⁻
H⁺
Br
Br
12
12i

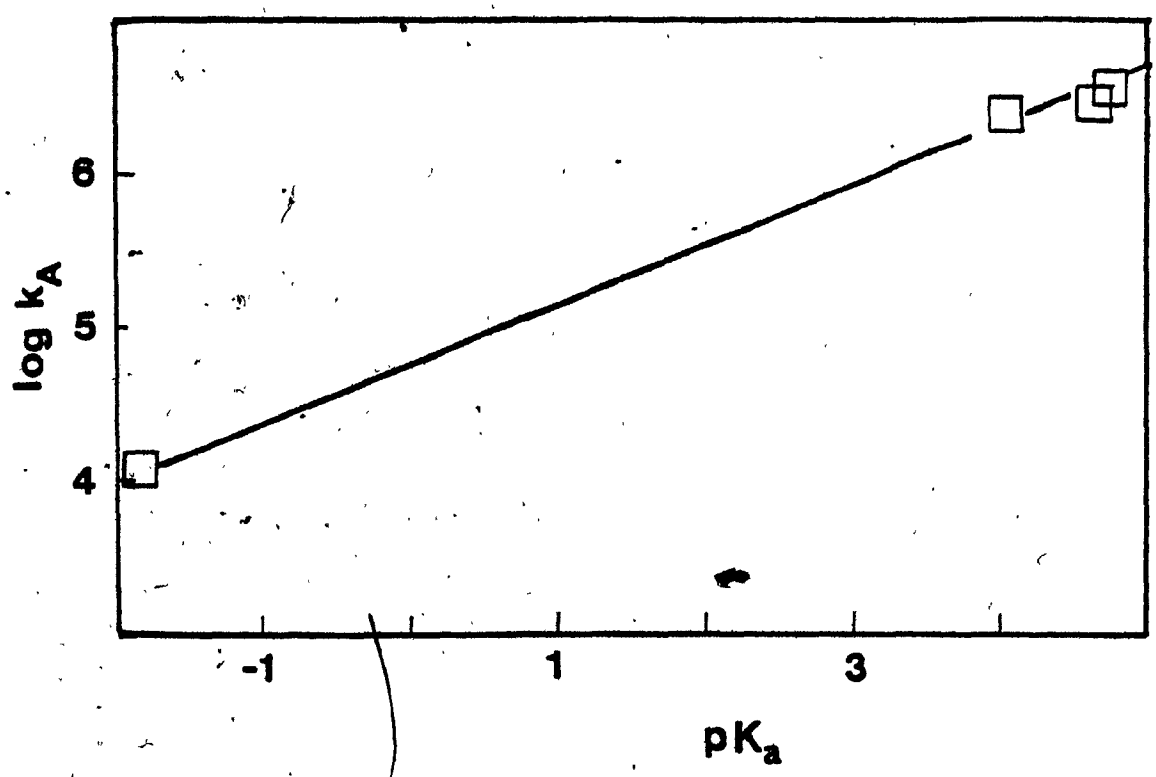
With the observed k_A values now, a more complete picture of the mechanism of bromination of phenol can be presented as shown in Scheme 20. The formation of the dienone (11) as well as the decomposition of this dienone are buffer catalyzed. The significant k_A values obtained in this study for all the three buffers can be explained as due to the base catalyzed attack of bromine on phenol (10) to form the 4-bromo-2,5-cyclohexadienone (11), thus avoiding the formation of the unstable protonated 4-bromo-2,5-cyclohexadienone (111). This eliminates from the traditional halogenation mechanism the first step as being the formation of a benzenonium ion type of intermediate. The data indicate that, at least in the halogenation of phenol, this unstable benzenonium type of intermediate is avoided by a concerted pathway forming the reasonably stable dienone directly (equation 78).



15 16 (78)

Figure 24

Bronsted Plot for the General Base-Catalyzed Bromine Attack on Phenol (10).



A plot of the log k_A values against the pK_a (Figure 24) gives a Bronsted β of 0.38 and from this value a rough estimation of the extent of proton transfer in the transition state can be assigned.[91] In the present case it indicates that proton transfer to the general base is about half transferred.

Nothing much can be said about the k_{HA} values as there is no trend in them with variation of pK_a. They may simply be artifacts resulting from experimental error. The pseudo-first-order rate constants measured at higher pH's and high buffer strengths are quite large and slight errors (even upto 5%) change the buffer slopes considerably and affect the k_{HA} values correspondingly. Moreover, reproducibility in the data was also a problem, presumably due to the same reasons.

Summary:

The attack of bromine on phenol shows buffer catalysis. From the observed data it is proposed that the first step in the bromination of phenol (the formation of dienone) is general base-catalyzed. This modifies the existing mechanism for the bromination of phenol which involves the formation of a benzenonium type of ion

intermediate. General base catalysis for the attack of bromine on phenol permits direct formation of the 4-bromo-2,5-cyclohexadienone (11) type of intermediate observed in Chapter 4. The Bronsted β value of 0.38 indicates that the proton of the phenolic hydroxyl is about half-transferred to the base in the transition state of the reaction (equation 78).

CHAPTER 7

Experimental

Materials:

Most of the substrates were of commercial origin and of the highest purity available and were used as received. Some of the substrates which were not purchased recently were recrystallized. The list of the substrates studied in this thesis, their origin, if recrystallized, the solvent and their melting points are given in Table XXXI. The buffer acids used in this study were also of highest quality available.

Product Analysis:

Product analysis studies were carried out for few of the substrates to ascertain the products formed under kinetic conditions.

(i) Bromination of salicylic acid:

To a 0.05 M solution of salicylic acid, 0.05 M solution of bromine (both in acetate buffer (pH 4.1) containing 0.1 M KBr) was added dropwise with continuous stirring. The white precipitate obtained was collected and the product was identified by NMR to be 5-bromosalicylic

Table XXXI

List of Compounds Studied in this Work

Serial Number	Compound	M.Pt. (^{o}C)
1.	Salicylic acid[a,d]	159 (159)
2.	o-Anisic acid (99%)[e]	99-100 (101)
3.	Methyl salicylate (99%)[f]	------
4.	5-Bromosalicylic acid[a,e]	167-169 (168-169)
5.	5-Sulphosalicylic acid (99.6%)[g]	
6.	5-Nitrosalicylic acid (98%)[h]	
7.	5-Formylsalicylic acid (97%)[e]	
8.	5-Methylsalicylic acid (98%)[e]	
9.	4-Methylsalicylic acid (99%)[e]	
10.	4-Chlorosalicylic acid (98%)[e]	
11.	p-hydroxybenzoic acid[i]	
12.	p-Anisic acid[b,e]	182 (185)
13.	Ethyl p-hydroxybenzoate[a,e]	115 (116-118)
16.	Phenol[c,d]	
17.	o-Cresol[e]	
18.	m-Cresol (99%; Gold Label)[e]	
19.	p-Cresol (99%; Gold Label)[e]	

Table XXXI (Cont'd)

Serial Number	Compound	M.Pt. (°C)
20.	p-t-Butyl phenol (99%)[e]	
21.	2,6-Dimethylphenol (99%, Gold Label)[e]	
22.	3,5-Dimethylphenol (99%)[e]	
24.	2,5-Dimethylphenol	
25.	Phenol d_6[j]	
26.	3-Bromo-4-hydroxybenzoic acid[a,k]	175-178 (177)

a. Recrystallized from water.

b. Recrystallized from methanol.

c. Recrystallized from benzene.

d. Obtained from Fisher Scientific Company.

e. Obtained from Aldrich Chemical Company.

f. Obtained from May and Baker.

g. Obtained from J.T. Baker Chemical Company.

h. Obtained from Fluka.

i. Obtained from Matheson, Coleman and Bell.

j. Obtained from MSD Isotopes.

k. Prepared by B. Kraus.

l. M. Pt. in parentheses refer to literature values (Ref. 105)

acid. M. Pt. of the product was 162-166 °C (lit. M. Pt. of 5-bromosalicylic acid is 168-169 °C).

(ii) Bromination of 5-bromosalicylic acid:

Equal volumes of 5-bromosalicylic acid (0.01M) and bromine (0.01M) both in buffered solutions (pH 4.5) containing 0.1M KBr were mixed with constant stirring. The solution was acidified with few drops of dilute hydrochloric acid to ensure maximum precipitation of the product. The melting point of the crude product was found to be 210 °C. The product was recrystallized from ethanol and the melting point of this product was 215 °C. The expected product 3,5-dibromosalicylic acid has a melting point of 223 °C.[107]

(iii) Bromination of p-hydroxybenzoic acid:

When equimolar (0.01M) amounts of p-hydroxy-benzoic acid and bromine were mixed (both in acetate buffer at pH 4.1 with 0.1M KBr) a white precipitate was formed which was isolated and recrystallized from hot water. From the melting point, T.L.C., and NMR spectra the product was identified to be 2,4,6-tribromophenol (yield 78%).

The product probably arises from two successive brominations and a bromodecarboxylation. At the pH used, the

reaction sequence can be written as:

p-Hydroxybenzoate ⟶ 3-bromo-4-hydroxybenzoate ⟶ 3,5-dibromo-4-hydroxybenzoate ⟶ 2,4,6-tribromo-phenol.

The rate constants for the second step is faster than for the first step (Table III). For the last step the bromination of 3,5-di- bromo-4-hydroxybenzoic acid, which involves a bromodecarboxylation, the measured rate constants (k_2^{obsd}) are 584 and 6140 M^{-1} s^{-1} at pH 0 and 1 respectively. These rate constants indicate that the reactivity of the anion of 3,5-dibromo-4-hydroxybenzoic acid towards bromine is essentially the same as that of the anion of 3-bromo-4-hydroxybenzoic acid. Thus, in the reaction of equimolar concentrations of p-hydroxybenzoic acid and bromine the initial products are more reactive towards bromine which leads to the formation of the 2,4,6-tribromo-phenol.

Accordingly, product studies were also carried out under kinetic conditions with 10-fold excess of substrate. To a solution of 0.01M p-hydroxybenzoic acid added 0.001M bromine solution both in acetate buffer (pH 4.1) containing 0.1M KBr and evaporated the mixture to

dryness. The residue was dissolved in methanol and analysed by TLC on silica using 90% methanol and 10% 0.02M KH_2PO_4 as eluent. From the R_f values it is clear that the product did not contain any tribromophenol (which was the product formed with 1:1 substrate and bromine). But the product could not be differentiated on the basis of R_f values from 3-bromo-4-hydroxybenzoic acid and 3,5-dibromo-4- hydroxybenzoic acid which are the other possible products anticipated. The product analysis was therefore done by GC/MS by trimethylsilating the residue obtained after drying the reaction mixture. The analysis showed the unreacted p-hydroxybenzoic acid, the 3-bromo-4-hydroxybenzoic acid and 3,5-dibromo-4-hydroxybenzoic acid as their bis-TMS derivatives. The ratio of 3-bromo-4-hydroxybenzoic acid to 3,5-dibromo-4-hydroxybenzoic acid was found to be 15:1, confirming the kinetic product with 10-fold excess of substrate to be 3-bromo-4-hydroxybenzoic acid i.e. the measured rate constants correspond to the monobromination of p-hydroxybenzoic acid.

Apparatus:

For kinetic studies an Aminco-Morrow stopped flow accessory[92] attached to an Aminco DW-2 UV-visible spectrophotometer operating in the dual wavelength mode was used. In this mode one monochromator is set at a reference wavelength where little or no change occurs and the second monochromator set at a convenient wavelength where a large change in absorbance is observed. By the means of a chopper, the reference and sample beams are alternately passed through the stopped flow observation cell which contains the sample. Normally the chopper operates at a speed of 250 Hz, but for reactions with half lives less than one second the kinetic chopper which operates at 1000 Hz is preferred. The DW-2 is balanced with mixed reactants in the observation cell to equalize the radiation intensities from both the monochromators and also to eliminate the absorbance due to the unreacted excess substrate as the reactions carried out were all of pseudo first-order type having substrate five or ten times in excess.

The advantages of using dual-wavelength mode can be listed as (i) use of reference solutions is eliminated; (ii) due to the use of same light source for illuminating

both the monochromators[93] the fluctuations in light intensity are minimized; (iii) artifacts due to light scattering in turbid solutions are minimized as both beams pass through the same observation cell;[93] (iv) in the dual-wavelength mode a difference signal is observed (instead of comparing the transmission ratio of the two absorption cells seen at the same wavelength) compensating for the fluctuations in the detector response and amplifier gain.[94,95]

For the reactions which were studied in this work one drive syringe was filled with 2 ml of the substrate solution in a selected buffer medium and the other syringe with 2 ml of bromine solution usually in the same medium (except when a buffer reacted with bromine). These two solutions were driven together under a nitrogen pressure of 58-60 p.s.i., into a 10 mm long observation cell. Under this nitrogen driving pressure the dead time of the system is estimated to be approximately 4 msec. The volume of the solution under observation at each time is 0.04 ml.[92] The stopping block in this system is controlled by a micrometer with an oscillscope trigger switch mounted in its tip. When the drive button is pushed in, the block advances as the two

solutions get mixed and simultaneously the micrometer switch is triggered, the data acquisition starts and the progress of the reaction can be observed on the oscilloscope.

Kinetic Solutions:

All buffer solutions were freshly prepared before use as it was found that they deteriorated with time. For pH dependence studies for reactions below pH 2, dilute aqueous sulphuric, hydrochloric, or perchloric acids were used. In case of hydrochloric acid they were usually diluted from 1M stock solutions (A & C American Chemicals). In the range of pH 2-7 buffers of constant ionic strength (0.01 M) were made up following Perrin's Table.[96] These include chloroacetate, acetate, succinate, and phosphate buffers. All solutions contain 0.1 M KBr (except where specified otherwise) so that the total ionic strength was 0.11 M except at lower pH's (< 2). Generally a stock solution 0.1M substrate in a suitable solvent was prepared and using appropriate aliquots of this stock solution were diluted with the desired pH solution. Similarly a bromine stock solution of 0.1 M in aqueous 0.1M KBr was diluted appropriately. Both the substrate and bromine solution dilutions were made just before the experiment was performed as it was found that bromine

reacted with certain buffers with time resulting in the absorbance change. The pH's of these solutions with the substrate and bromine in them were mixed 1:1 and measured with a Corning Digital 110 Expanded scale pH meter calibrated with appropriate standards.

For buffer catalysis studies, 0.3-0.1M aqueous buffers were prepared using the Henderson-Hasselbach equation (79) and employing the pK_a's corrected for 1M ionic strength. From these stock solutions buffers of lower

$$pH = pK_a + \log (A^-) / (HA) \qquad (79)$$

concentrations were made up with 1M NaCl solution for the experiments relating to the enolization of cyclohexadienones and with a mixture of 0.5M KBr and 0.5M NaCl for the debromination of ipso-dienones and the formation of dienone buffer catalysis studies. At lower pH's for these studies cyanoacetate (pK_a 2.23),[73] methoxyacetate (pK_a 3.52),[97] 3-chloropropionate (pK_a 3.93)[73] and propionate (pK_a 4.73)[98] buffers were employed and it was found that the former two buffers especially reacted with bromine. Therefore, when cyanoacetate and methoxyacetate buffers were used only the substrate was made up

in the buffer solutions (buffer concentrations being twice of what is desired) and mixed in the stopped-flow apparatus with bromine in 1M NaCl solution or a mixture of 0.5M KBr and 0.5M NaCl solution, as the case may be.

The substrate and bromine concentrations indicated in the tables refer to the final concentrations after mixing of the reaction solutions in the stopped flow apparatus.

Kinetic Procedure and Data Acquisition:

For all the kinetic runs the temperature in the observation cell was maintained at 25 ^{o}C. $\pm$ 0.1 ^{o}C using a Lauda RC - 20B constant temperature circulating water bath. Reactant solutions for pH dependence studies were 0.1M in KBr (except where specified otherwise). The addition of this large concentration of bromide ion has certain advantages:[40] (a) it swamps the effect of bromide ion produced in the reaction, (b) it increases the stability of bromine solutions since much of the bromine is present in the form of tribromide ion (c) it reduces the rate of reaction by reducing the free bromine concentration, (d) it facilitates spectrophotometric measurement of rates since tribromide ion has a larger extinction coefficient than bromine at their

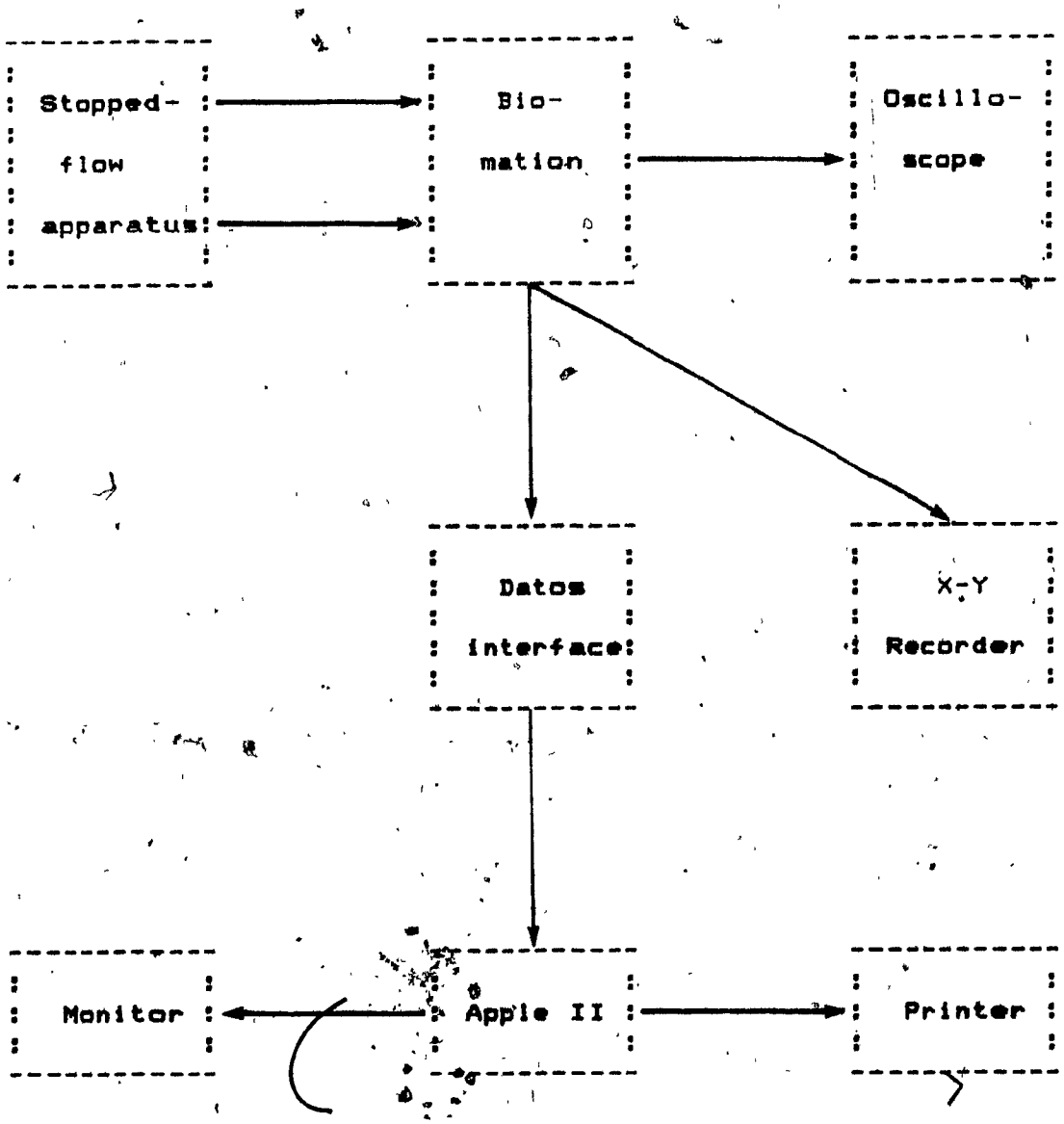
respective λ_{max} and (e) it ensures that the ionic strength is high and constant (0.11M) for all the pH-dependence studies in buffer solutions.

Bromination reactions were followed by monitoring the decrease in tribromide absorbance (λ_{max} for Br_3^- is 266 nm and log ε is 4.54).[99] For the pH-dependence studies of bromination of salicylic acid (5), p-hydroxybenzoic acid (1) and their derivatives and buffer catalysis studies involving the formation of the dienone of phenol, the sample monochromator was set between 267-280 nm (depending upon where the best signal to noise ratio was observed), with the reference monochromator at 340-350 nm. For experiments dealing with the decay of the cyclohexadienone intermediate and debromination of the ipso-dienones the sample monochromator was set between 235-250 nm (depending upon where the maximum absorbance change was observed) and the reference monochromator at 320 nm where there was little or no change.

All reactions were carried out under pseudo first-order conditions. Generally the concentrations of substrate were 5×10^{-4} M and bromine 5×10^{-5} M (after 1:1 mixing in the stopped-flow apparatus). For fast reactions these concentrations were reduced by 5 times.

Figure 23

Stopped-Flow Data Acquisition System.



For reactions with a half-life of less than ca 20 seconds, a data acquisition system was used to monitor the kinetics (Figure 25). For each reaction, the output voltage of the DW-2 (proportional to absorbance at 2V/A) was recorded on a Biomation 605 digital wave form recorder (8-bit resolution). This stored signal was viewed on a Tektronix 2215 60 MHz oscilloscope. Acceptable traces were plotted from the Biomation onto the Aminco X-Y recorder for the purpose of records. From the Biomation the stored digitized traces (2048 points) were transferred serially at 9600 baud via a Datos 305 interface to an Apple II micro computer. Every 20th point was extracted and displayed by the Apple on the monitor, a total of 100 points. From these an infinity value was estimated as the average of the last ten points. The rate constants for a specific run was calculated from 15-40 points spanning about 90% of the reaction using the TRist programme (described later).

Slow reactions with a half-life greater than ca 20 seconds were recorded directly onto an X-Y recorder 20-30 points, corresponding to 90% reaction, were obtained by hand digitising the plots and rate constants were determined by analysing this data using New ist programme on the Cyber 170 mainframe computer or the First programme on the Apple.

The pseudo-first order rate constants were obtained as the average of 3-5 runs which differed by <5%. Individual first-order rate constants were obtained from least-squares analysis of $\ln(A-A_\infty)$ Vs time. The runs which gave r >0.9995 in least-squares analysis were printed out.

Computer Programmes:

First order rate constants were calculated by the three programmes TRist, Newist and FIRST, all of which use the Guggenheim, the Swinbourne and the Normal (with Swinbourne calculated infinity) and Normal (with observed infinity) methods. It was observed in the majority of the cases that the first-order rate constants obtained by all four methods varied only slightly (< 5%). For pH-rate profiles a PROFIT programme was used where calculations are done by fitting appropriate rate equations to the experimental points. This is an iterative programme which makes use of standard non-linear least-squares techniques[100] and gives the best curve to a given set of experimental data.

All of these computer programmes were written in Basic and machine language by Prof. O.S. Tee.

Treatment of Kinetic Data:

As mentioned earlier the first-order rate constants were calculated by the computer programmes using various methods. The simultaneous use of different methods provides a useful check on the quality of the data. A brief outline of each method is given in this section.

" Normal " Treatment of Kinetic Data:

For a first-order reaction the rate may be represented as

$$\frac{dx}{dt} = k_1 (b-x) \qquad (80)$$

where b refers to the initial concentration of the reactant B, x represents the amount B which has reacted by time t and k_1 is the first-order rate constant.

Equation 80 can be integrated to give equation 81

$$k_1 t = \ln \frac{b}{(b-x)} \qquad (81)$$

For a pseudo first-order reaction which goes to completion there is generally one of the reactants in large excess with respect to the concentration of second reactant. Progress of such a reaction (equation 82) may be monitored spectrophotometrically

$$A + B \longrightarrow P \qquad (82)$$

if the Beer-Lambert Law is obeyed. For a cell of unit thickness, the following relations should hold good:

$$A_0 = \varepsilon_A a + \varepsilon_B b \quad (83)$$

$$A = \varepsilon_A (a-x) + \varepsilon_B (b-x) + \varepsilon_P x \quad (84)$$

and

$$A_\infty = \varepsilon_A (a-b) + \varepsilon_P b \quad (85)$$

where A_0, A_∞ and A refer to the absorbances at time t=0, at t= ∞ , and at time t, respectively. ε_A, ε_B and ε_P represent the extinction coefficients of the reactants A and B and the product P at the analytical wavelength used.

Under pseudo first-order conditions (a >> b > x) combination and rearrangement of equations 83 - 85 result in

$$(b-x) = \frac{A - A_\infty}{\varepsilon_B - \varepsilon_P} \quad (86)$$

Equation 81 can now be rewritten as

$$k_1 t = \ln \frac{b}{(b-x)} = \ln \frac{(A_0 - A_\infty)}{(A - A_\infty)} \quad (87)$$

or

$$\ln (A - A_\infty) = \ln (A_0 - A_\infty) - k_1 t \quad (88)$$

which can also be expressed as

$$(A - A_\infty) = (A_0 - A_\infty) e^{-k_1 t} \quad (89)$$

From equation 88 a plot of ln $(A - A_\infty)$ vs time

should give a straight line with a negative slope equal to k_1. The computer programmes used least-square analysis to evaluate k_1 from lines with a correlation coefficient > 0.9995 for data corresponding to about 90% of reaction.

This type of analysis requires an accurate measurement of A_∞ since any small discrepancies in A_∞ value may not affect the least-squares analysis particularly but can cause significant changes in the k_1 value. (Collins estimates that an error of one part in A_∞ can affect the rate constant up to fourteen times).[102] Therefore, in order to accurately estimate A_∞ all runs were monitored for more than 10 half-lives (> 99.9% reaction). Towards the end of the reaction the absorbance change generally becomes small relative to the noise and so A_∞ values obtained by this method were compared to A_∞ values obtained by Swinbourne method. It was observed that to a large extent the A_∞ values obtained by these two methods differed very little.

Swinbourne Treatment of Data[103,104]

This treatment makes use of the integrated rate equation, equation 89. Consider a first-order reaction where A_1, A_2, ------- A_n refer to the absorbance values at times t_1, t_2, ------- t_n and A_1', A_2', ------- A_n' are a second

set of readings at $t_1 + T$, $t_2 + T$, ------ $t_n + T$ times where T is constant. The first set of readings can be represented by equation 89 i.e.

$$(A - A_\infty) = (A_0 - A_\infty)\, e^{-k_1 t} \qquad (89)$$

and the second set of data by equation 90

$$(A' - A_\infty) = (A_0 - A_\infty)\, e^{-k_1 (t + T)} \qquad (90)$$

Dividing equation 89 by 90 gives

$$\frac{(A - A_\infty)}{(A' - A_\infty)} = e^{k_1 T} \qquad (91)$$

and therefore

$$A = A_\infty (1 - e^{k_1 T}) + A' e^{k_1 T} \qquad (92)$$

Thus a plot of A versus A' should give a straight line with slope = $e^{k_1 T}$ and intercept = $A_\infty (1 - e^{k_1 T})$. This enables the k_1 to be calculated from the slope and A_∞ from the following equation 93

$$A_\infty = \frac{\text{intercept}}{(1 - \text{slope})} \qquad (93)$$

The value of T should be between one half and one half-life and the data should span beyond two half-life periods. The values of A_∞ obtained by this method were also introduced into the normal method and values of k_1 were calculated.

Guggenheim Treatment of Data:[101,104]

This method allows the calculation of a first-order constant without using A_∞ values. Subtracting equation 89 from 90 gives

$$(A' - A) = (A_0 - A_\infty) e^{-k_1 t} (e^{-k_1 T} - 1) \quad (94)$$

and so

$$\ln (A' - A) = \ln (A_0 - A_\infty)(e^{-k_1 T} - 1) - k_1 t \quad (95)$$

which can be written as

$$\ln (A' - A) = \text{constant} - k_1 t \quad (95)$$

Linear regression analysis of ln (A' - A) against t will result in a straight line of slope $-k_1$. For best results the data should cover at least two half-lives and T should be between one half and one half-life, as with the Swinbourne treatment.

The first-order rate constants obtained for this thesis were all calculated from the data by the " Normal Method " using observed A_∞. The observed first-order rate constants cited are the average of 3-5 runs differing by < 10% and usually < 5%. Note, however, that the use of Guggenheim and Swinbourne Methods was very useful for detecting drifting infinity values. It led to our discovery of transient cyclohexadienones!

REFERENCES

REFERENCES

1. Rainsford, K.D. Aspirin and the Salicylates Butterworths & Co. Ltd. 1984.

2. Delary, E.J.; Massil, S.E.; Shi, G.Y.; Kletz, I.M. Arch. Biochem. Biophys. 1984, 228 (2), 627.

3. Ershov, V.V.; Volod'kin, A.A.; Bogdanov, G.N. Russ. Chem. Rev. 1963, 75.

4. Ugland, K.; Lundanes, E.; Greibrokk, T.; Bjorseth, A. J. Chromatogr. 1981, 213, 83 and refernces therein.

5. Ander, P.; Ericksson, E.E.; Kolars, M.C.; Kringstad, K.; Rannug, V.; Ramel, C. Sv. Pappertidin 1977, 80, 454; Chem. Abs. 1978, 88, 78652 a.

6. Bjoreseth, A.; Carlberg, G.E.; Moller, M. Sci. Total Environ. 1979, 11, 197; Chem. Abs. 1979, 90, 181055 y.

7. Carlberg, G.E.; Gjos, N.; Moller, M.; Gustavsen, K.O.; Tveten, G.; Renberg, L. Sci. Total Environ. 1980, 15, 3; Chem. Abs. 1980, 93, 209709 c.

8. Marsili, G.; Cignitti, M. Gazz. Chim. Ital. 1979, 109, 553; Chem. Abs. 1980, 93, 70734 m.

9. Bell, R.P.; Rawlinson, D.J. J. Chem. Soc. 1961, 63.

10. Paventi, M. Ph.D. Thesis Concordia Univ., 1984.

11. Kulic, J.; Vecera, M. Collect. Czech. Chem. Commun. 1974, 39, 171.

12. Volod'kin, A.A.; Ershov, V.V. Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk. 1962, 2022,; Chem Abs. 1963, 58, 11251 c.

13. Ershov, V.V.; Nikiforov, G.A. Russ. Chem. Rev. 1966, 35, 817.

14. Robertson, P.W.; de la Mare, P.B.D.; Swedlund, B.E. J. Chem. Soc. 1953, 782.

15. de la Mare, P.B.D.; Singh, A. J. Chem. Soc. (B) 1971, 1122.

16. de la Mare, P.B.D.; Singh, A. J. Chem. Soc. Perkin. Trans. 2 1972, 1801

17. de la Mare, P.B.D.; el Dusoqui, O.M.H.; Tillet, J.G.; Zeltner, M. J. Chem. Soc. 1964, 5306.

18. de la Mare, P.B.D.; Singh, A. J. Chem. Soc., Perkin Trans. 2 1973, 59.

19. Baciocchi, E.; Illuminati, G. J. Am. Chem. Soc. 1967, 89, 4017.

20. Fyfe, C.A.; Van Veen, L. Jr. J. Am. Chem. Soc. 1977, 99, 3366.

21. Fyfe, C.A.; Cocivera, M.; Damji, S.W.H. Acc. Chem. Res. 1978, 11, 277.

22. Fischer, A.; Henderson, G.N. Can. J. Chem. 1983, 61, 1045.

23. Brittain, J.M.; de la Mare, P.B.D.; Isaacs, N.S.; Mc. Intyre, P.D. J. Chem. Soc. Perkin Trans. 2 1979, 933.

24. Brittain, J.M.; de la Mare, P.B.D.; Newman, P.A. J. Chem. Soc. Perkin Trans. 2 1981, 32.

25. Brittain, J.M.; de la Mare, P.B.D.; Newman, P.A.; Chin, W.S. J. Chem. Soc. Perkin Trans. 2 1982, 1193.

26. Coombes, R.G.; Golding, J.G.; Hadjigeorgiou, P. J. Chem. Soc. Perkin Trans. 2 1979, 1451.

27. Bloomfield, C.; Manglik, A.K.; Moodie, R.B.; Schofield, K.; Tobin, D.G. J. Chem. Soc. Perkin Trans. 2 1983, 75.

28. Toullec, J. Adv. Phys. Org. Chem. 1982, 18, 1 and references therein.

29. Haspra, P.; Sutter, A.; Wirz, J. Angew. Chem. Int. Ed. Engl. 1979, 18, 617.

30. Capon, B.; Rycroft, D.S.; Watson, T.W. J. C. S. Chem. Commun., 1979, 724.

31. Chiang, Y.; Kresge, J.A.; Wirz, J. J. Am. Chem. Soc. 1984, 106, 6392.

32. Jencks, W.P.; Regenstein, J. In "Handbook of Biochemistry and Biology", 3rd Edn., Fassman, G.D., Ed.; CRC Press: Cleveland, Ohio, 1976, Vol I, p 313-314.

33. Hibbert, F. Acc. Chem. Res. 1984, 17, 115.

34. Rao, T.S.; Mali, S.I. J. f. prakt. Chem. 1974, 316, 1047.

35. Dunn, G.E.; Kung, F.L. Can. J. Chem. 1966, 44, 1261.

36. Dunn, G.E.; Penner, T.L. Can. J. Chem. 1967, 45, 1699.

37. Tee, O.S.; Iyengar, N.R.; Paventi, M. J. Org. Chem. 1983, 48, 759.

38. Tee, O.S.; Iyengar, N.R. J. Am. Chem. Soc. 1985, 107, 455.

39. Tee, O.S.; Iyengar, N.R.; Kraus, B. J. Org. Chem. 1985, 50, 973.

40. Tee, O.S.; Berks, C.G. J. Org. Chem. 1980, 45, 830.

41. Aaron, J.J.; Dubois, J.E. Bull. Soc. Chim. Fr. 1971, 603.

42. Tee, O.S.; Bennett, J.M. Unpublished results.

43. Leffler, J.E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963, p 203-210.

44. Ridd, J.H. Adv. Phys. Org. Chem. 1978, 16, 1.

45. Perrin, D.D.; Dempsey, B.; Serjeant, E.P. 'pK_a Prediction for Organic Acids and Bases'; Chapman and Hall: London, 1981, p 47.

46. Kortum, G.; Vogel, W.; Andrussow, K. Pure Appl. Chem. 1961, 1, 190.

47. Ref 45, p 137.

48. Ref. 45, p 111.

49. Tee, O.S.; Swedlund, B.E. Can. J. Chem. 1983, 61, 2171.

50. Hine, J. 'Structural Effects on Equilibria in Organic Chemistry'; Kreiger: New York, 1981, p 67.

51. Perrin, D.D. Nature 1958, 741.

52. Hibbert, F.; Awwal, A. J. Chem. Soc. Perkin Trans. 2 1978, 939.

53. Bell, R.P., 'The Proton in Chemistry'; Cornell University Press, Ithaca, N.Y., 1973, p 131.

54. Eigen, M. Angew. Chem. Int. Ed. Engl. 1964, 3, 1.

55. Vitullo, V.P.; Grossman, N. J. Am. Chem. Soc. 1972, 94, 3844.

56. Cook, K.L.; Waring, A.J. J. Chem. Soc. Perkin Trans. 2 1973, 84.

57. " Dictionary of Organic Compounds ", 4th Edition, Vol I Eyre and Spottiswoode, London, 1965.

58. " Stability Constants of Metal-Ion Complexes ", Special Publication No. 17, Chemical Society, London, 1964.

59. Laughton, P.M.; Robertson, R.E. In " Solute Solvent Interactions "; Coetzee, J.F.; Ritchie, C.D. Eds.; Marcel Dekker: New York 1969, Chapter 7.

60. Modro, A.; Schmid, G.H.; Yates, K. J. Org. Chem. 1979, 44, 4221.

61. Capon, B. In " Proton Transfer Reactions "; Caldin, E.; Gold, V. Eds., Chapman and Hall: London; 1975, Chap.11.

62. Kirby, A.J. Adv. Phys. Org. Chem. 1980, 17, 183.

63. de la Mare, P.B.D.; Acc. Chem. Res. 1974, 7, 361.

64. Miller, B. J. Am. Chem. Soc. 1970, 92, 6246.

65. Ibid p 6252.

66. Quinkert, G.; Dürner, G.; Kleiner, E.; Haupt, E. Leibfritz, D. Angew. Chem. Int. Ed. Engl. 1979, 18, 556.

67. Lasne, M.C.; Ripoll, J.L.; Denis, J.M. Tetrahedron Lett. 1980, 21, 463.

68. Moore, J.W.; Pearson, R.G. " Kinetics and Mechanism "; Wiley: New York, 1981, p 290.

69. Miller, B. Acc. Chem. Res. 1975, 8, 245.

70. Jencks, W.P. Catalysis in Chemistry and Enzymology McGraw-Hill : New York 1969, p 198.

71. Ibid, p 240.

72. Ibid, p 97-98.

73. Funderburk, L.H.; Aldwin, L.; Jencks, W.P. J. Am. Chem. Soc. 1978, 100, 5444.

74. Gilbert, H.F.; Jencks, W.P. J. Am. Chem. Soc. 1982, 104, 6769.

75. Ref. 28, p 8.

76. Grovenstein, Jr. E.; Aprahamian, N.S.; Bryan, C.J.; Gnanapragasam, N.S.; Kilby, D.C.; Mc. Kelvey, Jr. J.M.; Sullivan, R.J. J. Am. Chem. Soc. 1973, 95, 4261.

77. Cook, K.L.; Waring, A.J.; Tetrahedron Lett. 1971, 36, 3359.

78. Vitullo, V.P. J. Org. Chem. 1969, 34, 224.

79. Kresge, A.J.; Mylonakis, S.G.; Sato, Y.; Vitullo, V.P. J. Am. Chem. Soc. 1971, 93, 6181.

80. Kresge, A.J.; Chen, H.J.; Hakka, L.E.; Kouba, J.E. J. Am. Chem. Soc. 1971, 93, 6174.

81. Chiang, Y.; Kresge, A.J.; Tang, Y.S.; Wirz, J. J. Am. Chem. Soc. 1984, 106, 460.

82. Tapuhi, E.; Jencks, W.P. J. Am. Chem. Soc. 1982, 104, 5758.

83. Guthrie, J.P.; Cossar, J.; Klym, A. J. Am. Chem. Soc. 1984, 106, 1351.

84. Cox, R.A.; Smith, C.R.; Yates, K. Can. J. Chem. 1979, 57, 2952.

85. Albery, W.J. J. Chem. Soc. Faraday Trans. 1 1982, 78, 1579.

86. Jencks, W.P. Acc. Chem. Res. 1976, 9, 425.

87. Guthrie, J.P. J. Am. Chem. Soc. 1980, 102, 5286.

88. Jencks, W.P. J. Am. Chem. Soc. 1972, 94, 4731.

89. Ridd, J.H. Adv. Phys. Org. Chem. 1978, 16, 1.

90. Chattopadhyaya, M.C.; Singh, R.S. Ind. J. Chem. 1980, 19A, 141.

91. Kresge, A.J. In "Proton Transfer Reactions", Caldin, E.F.; Gold, W., Eds.; Chapman and Hall: London, 1975, Chap. 7.

92. Morrow, J.J. Chem. Instrum. 1970, 2, 375.

93. Chance, B. Rev. Sci. Inst. 1954, 22, 634.

94. Rikmenspoel, R. Appl. Opt. 1964, 3, 351.

95. Pecsok, R.L.; Shields, L.D. "Modern Methods of Chemical Analysis", Wiley, New York, 1968, p 181.

96. Perrin, D.D. Aust. J. Chem. 1963, 16, 572.

97. Sayer, J.M.; Jencks, W.P. J. Am. Chem. Soc. 1977, 99, 464.

98. Ref. 32, p 309.

99. Pink, J.M. Can. J. Chem. 1970, 48, 1169.

100. Daniel, C.; Wood, F.S. " Fitting Equations to Data ", 2nd Ed., John Wiley & Sons, New York, 1980.

101. Laidler, K.J. " Chemical Kinetics ", McGraw Hill, New York, 1965.

102. Collins, C.J. Adv. Phys. Org. Chem. 1964, 2, 1.

103. Swinbourne, E.S. J. Chem. Soc. 1960, 2371.

104. Swinbourne, E.S. " Analysis of Kinetic Data ", Thomas Nelson & Sons Ltd., London, 1971, Section 4.1.

105. " CRC Handbook of Chemistry and Physics " 52nd Edn., 1971-72, Pub. by The Chemical Rubber Co., Cleveland, Ohio.

106. Sorenson, J.R.J. Chemistry in Britain 1984, 20, 1110.

107. The Merck Index, 9th Edn., 1976, Pub. by Merck & Co., Inc, N.J., U.S.A.

108. Fischer, A.; Henderson, G.N. Can. J. Chem. 1979, 57, 552.