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The Effect of α-Cyclodextrin on the Bromination of Phenols

A Thesis

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The Department

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ABSTRACT

The Effect of α-Cyclodextrin on
the Bromination of Phenols

Janice M. Bennett

α-Cyclodextrin accelerates the rate of bromination of phenol and 2,3 and 4-substituted phenols and their anions in aqueous KBr solutions (0.05-0.1M). A catalytic pathway involving complexed bromine reacting with free substrate appears to be present. This pathway exceeds the rate reductions due to complexation of the tribromide ion, bromine and substrate. Phenol-CD dissociation constants measured by equilibrium and kinetic methods range between 1.4-83mM.

α-Cyclodextrin also exhibits remarkable rate acceleration of the debromination of transient 4-alkyl-2,5-cyclohexadienones formed during the bromination reaction of p-alkylphenols. Kinetically determined ipso-dienone-CD dissociation constants range between 0.7-5mM. A catalytic pathway, consistent with the second-order bromination pathway, is thought to involve complexed bromide ion reacting with uncomplexed intermediate. Very modest rate perturbations were observed in the α-cyclodextrin-mediated

enolization of 2,5-cyclohexadienones in KBr solutions.

The catalytic effects which are observed are thought to be due to a non-covalent pathway for the bromination involving the parent phenols, their ionized forms and the ipso-dienone debromination mechanism. That is, the effects of the cyclodextrin are not due to any covalent interaction with the reactants but rather it provides a slightly different environment in which the reaction takes place.

Dedication

I'd like to thank all those individuals who have contributed to my knowledge and achievements. Special thanks go to Dr. O.S. Tee for developing my scientific curiosity and interests.

I'd like to thank Jim for his unrelenting support of my dreams.

Thanks for the memories gang!!!

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Introduction

The formation of inclusion complexes which undergo enzyme-like reactions has stimulated much research in recent years. Of particular interest are the water-soluble cyclodextrins which are capable of forming inclusion complexes with a variety of compounds. Cyclodextrins and their chemistry have been the subject of several reviews[1-6] and numerous publications.

Cyclodextrins

As their name may imply, cyclodextrins are composed of an integral number of 1,4-linked glucose units joined in a cyclic fashion. The most common are α-, β- and γ-cyclodextrin having 6,7 and 8 glucose units respectively.

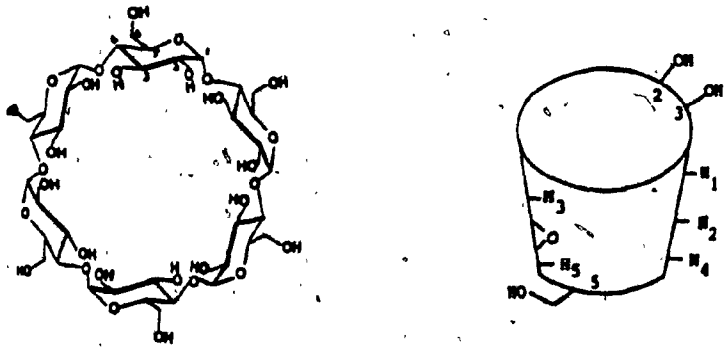


Figure 1. α- and β-Cyclodextrin[7]

The numerous physical properties of the cyclodextrins have been well characterized in the literature.[1,4] X-ray crystallographic analysis[8] of these compounds has confirmed the presence of a cavity wherein complexation occur. In the case of α-cyclodextrin it has been shown that the cavity

has a depth of 7Å and an internal diameter of 4.5Å.[1]

Inclusion Compounds

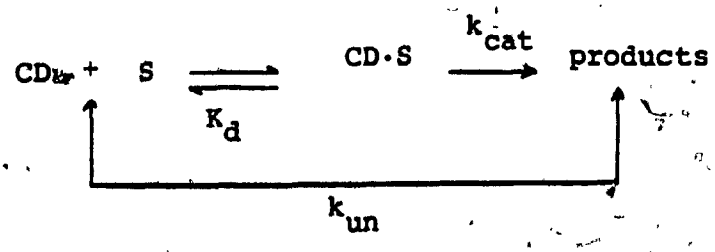
Cyclodextrins markedly improve the solubility of many compounds in aqueous solution.[1] Hydrophobic inclusion has been reported for a variety of organic and inorganic compounds, ranging in size from large aromatic hydrocarbons to small anionic species.[9] Evidence supporting the presence of a hydrophobic cavity in which compatible "guests" may reside has been found principally from ultraviolet[10,11] and ^{1}nmr spectroscopic studies.[12] When monitoring the effect of α-cyclodextrin on the UV spectrum of p-t-butylphenol in an aqueous medium Bender[10] and co-workers found a spectral shift due to the cyclodextrin/ p-t-butylphenol inclusion complex formed. This complex showed UV spectral similarities to p-t-butylphenol in dioxane, strongly suggesting binding in the cyclodextrin cavity.

The extent or strength to which encapsulation takes place is often expressed as a dissociation constant (= 1/formation constant). The most widely-used method of determining such constants has been using ultra-violet absorption spectroscopy. Here, significant changes with respect to absorption and λ_{max} may take place upon complexation.

Catalytic Effects

Perhaps the most important phenomenon pertaining to the cyclodextrins has been their effect on reactivity. These

compounds show remarkable catalysis, and in some cases, inhibitory properties when added to a variety of reactions. The early research of Bender's group[10,13] involved hydrolytic reactions in the presence of α- and β-cyclodextrin and the possible catalytic effect that these compounds possess. In studying their effect on the hydrolysis of a group of phenyl esters they found that the rate of hydrolysis underwent slight to dramatic acceleration, depending on the ester. The rate enhancements were attributed to covalent catalysis[14] by the respective cyclodextrin.



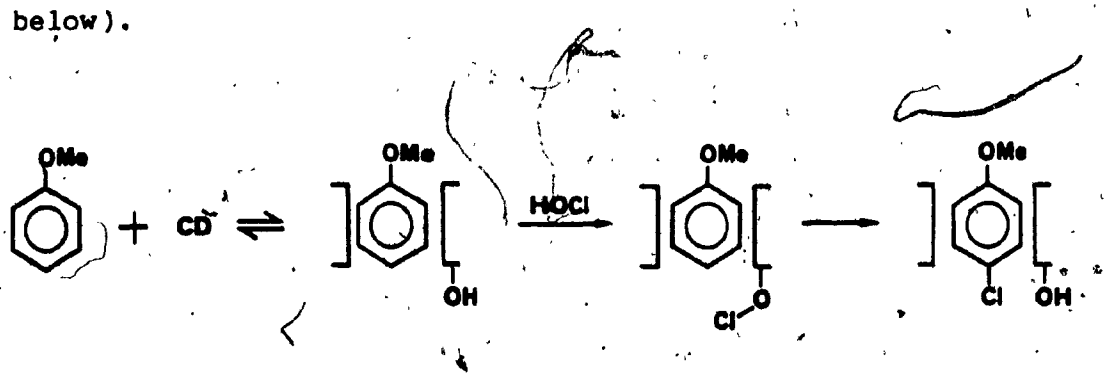
Scheme 1 Covalent Catalysis by Cyclodextrin[1]

Once the new inclusion complex between the phenyl ester and the cyclodextrin is formed, an ionized secondary hydroxyl group (2- or 3-OH) of the cyclodextrin forms a covalent intermediate with the included ester which subsequently hydrolyses to the acid product.

In addition to covalent catalysis, the cyclodextrins were found to exhibit selectivity between different aryl ester isomers. It was found generally that the meta isomer displayed the larger catalytic effect. In addition, there was no relationship between the electronic character of the

substituent and the acceleration rate. Consequently it was concluded that the position of the substituent largely governs the selectivity of cyclodextrins towards different substrates. More recently in this laboratory, it was shown that there is covalent catalysis by cyclodextrins in the hydrolysis of aspirin derivatives in aqueous base.[15]

Although many of the reported reactions involving cyclodextrins have involved hydrolysis, Breslow and Campbell[16] studied the chlorination of anisole by hypochlorous acid in aqueous solutions containing α- or β - cyclodextrin. In both cases, complexation of anisole occurred and it was proposed that chlorination proceeds via a hypochlorite ester of the respective cyclodextrin (see below).



Scheme 2 The Chlorination of Anisole[16]

With the reaction proceeding via this mechanism, chlorination favours para substitution due to a proximity effect while restricting or suppressing formation of the ortho chlorinated product. The latter arises since the ortho positions are hindered once the anisole is encapsulated.

Experimentally, it was shown that with increasing concentrations of the cyclodextrin, a dramatic increase in the para/ortho ratio occurs with corresponding slight increases in the rate of chlorination. This and other evidence supports the reaction mechanism involving a hypochlorite ester of the cyclodextrin.[16]

More recent work involving cyclodextrins has concentrated on the degree to which these compounds can accelerate a given reaction. Much of the published research has focussed on modifying the cyclodextrin functionality whereby rate effects, enantio- and stereoselectivity may approach enzymatic proportions. These structural changes are aptly referred to as "host design". Breslow[17] et al have recently adapted the functionality of the cyclodextrins so as to mimic the enzyme ribonuclease which catalyses the hydrolytic cleavage of RNA. In their study, Breslow's group mounted the principle catalytic groups of ribonuclease onto the cyclodextrin, causing both aryl phosphate substrate binding and catalyzed reactions within the substrate-CD complex showing high positional selectivity.

In general, most reactions involving cyclodextrin assisted catalysis have shown modest accelerations. By far the most catalysed reaction found to date has been that involving carefully-designed derivatives of ferrocene[18] where ester cleavage in the presence of α-cyclodextrin has shown rate accelerations approaching six-million fold! In addition, the chirality of the cyclodextrin nucleus leads

to substantial enantioselectivity, with a ratio of sixty-five in favour of one mirror image isomer over the other.[18]

From the foregoing one can appreciate the important features of the cyclodextrins in their selectivity and rate accelerating potential in a variety of reactions. Their ability to perform as "artificial enzymes" may in the future play an important role in chemical synthesis as well as having potential therapeutic applications.[17]

In addition to covalent catalysis, cyclodextrins can accelerate certain reactions via non-covalent interactions.[1] In these cases, the apolar cavity of the cyclodextrin provides a reaction medium different from the bulk solvent where the substrate reacts. Non-covalent catalysis may be attributed to a microsolvent effect based on the apolar environment of the cavity as well as to the intrinsic geometric requirements governing inclusion.

One such example of non-covalent catalysis involves the decarboxylation of β-keto acids.[19] In this reaction, the unimolecular rate-determining cleavage of the α-carbon/carboxylate bond shows a large dependence on solvent polarity. In the presence of cyclodextrins, one sees a rate enhancement due to the ether-like environment of the cyclodextrin cavity. Support for the reaction taking place via a non-covalent catalytic pathway is based on three features a) both the uncatalysed and catalysed rate constants k_{un} and k_2 follow the Hammett relationship, b) substituent

positioning (ortho, meta, para) had little effect on the acceleration rate and c) the rate constants were independent of medium effects such as pH and buffer catalysis.

Non-covalent catalysis by cyclodextrins may depend not only on the apolar cavity characteristics but also on conformational effects brought about by inclusion. Here, due to spatial restrictions, cyclodextrins may preferentially encapsulate one conformer of a substrate over another thereby inducing acceleration or inhibition. Such non-covalent catalysis has been observed in the cyclodextrin catalyzed cleavage of certain alkyl esters.[13]

Effects on Anisole Bromination[20,21]

Our initial investigation regarding the cyclodextrins and their effect on reactivity concerned the extent to which α-cyclodextrin effects the electrophilic attack of bromine on p-nitrophenol and phenol in aqueous solutions. At the time it seemed like a reasonable course to pursue since it was known[12,16] that inclusion complexes between α-cyclodextrin, the parent and ionized form of the substrate are formed. Moreover, dissociation constants had been determined and information regarding the kinetics of complexation of p-nitrophenol had been documented.[11]

Preliminary kinetic studies indicated that the α-cyclodextrin mediated bromination of simple phenols was much more complex than originally anticipated. Consequently, we studied the bromination of anisole and p-methylanisole in the presence of α-cyclodextrin[20,21] thereby avoiding any

effects due to ionizable phenols and their inherent pH-rate dependence.

Even the simple bromination of anisole proved to be complex in nature in the presence of α-cyclodextrin due to the formation of several inclusion complexes under the experimental conditions. The overall effect of α-cyclodextrin was to substantially reduce the rate of bromination of both anisole and p-methylanisole. It was shown that most of the retardation was due to the formation of a tribromide ion inclusion complex which exceeds the other encapsulations in strength.[20,21]

In the case of anisole, the extent of rate inhibition was much less than expected from the measured dissociation constants of the inclusion complexes formed. This phenomenon was attributed to a second bromination pathway involving α-cyclodextrin. This catalytic mechanism was concluded to be either one of two kinetically indistinguishable pathways, the first possibility being complexed substrate reacting with "free" bromine and the latter being free substrate reacting with encapsulated bromine. For p-methylanisole, the presence of a second bromination pathway was not required by the data.[20,21]

The Bromination of Phenols

This reaction has been extensively researched by numerous groups. De la Mare [22] and co-workers studied the rate of bromination of phenol in anhydrous acetic acid. Under aqueous perchloric acid conditions, Bell and Rawlinson [23] looked at the bromination of phenols and discovered that two species react with molecular bromine: the parent phenol and the corresponding ionized phenol. In addition the tribromide ion, in equilibrium with molecular bromine, reacts with the phenoxide ion via an additional pathway. The major drawback to the reported results lie in the limited pH range studied due to the increasing reactivity of phenol with increasing pH.

Kulic and Vecera[24] studied the kinetics of bromination of a variety of p-substituted phenols also under aqueous perchloric acid conditions. Of particular interest to this study are the rate constants for the bromination of the respective phenols and phenolates where it was concluded that based on the Hammett correlation, the parent phenol was the more selective species.

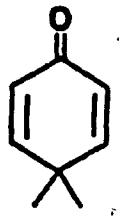
More recently Paventi[25] studied the bromination of phenol and various substituted phenols in aqueous solutions of pH 0-7. The reaction was found to be overall second-order, first order in each reactant, showing agreement with earlier reports. Product analysis showed the major product of phenol bromination to be the p-bromophenol (82%). Although the reported second-order rate constant for bro-

mination was slightly higher in magnitude than the literature result,[23] it would seem the more recently reported results are more reliable. Indeed, Bell and Rawlinson[23] admit that their value is of low reliability, being obtained near the limit of the technique they employed.

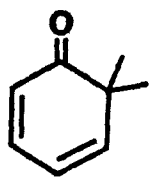
Cyclohexadienone Intermediates

The formation of cyclohexadienone intermediates during reactions involving phenols has often been suggested yet there have been relatively few studies of cyclohexadienone formation in the literature. Stable intermediates of this type have been spectrophotometrically observed during the bromination of various 2,6-dialkylphenols. Ershov and coworkers[26] isolated the cyclohexadienone produced during the bromination of 2,6-di-t-butylphenol. More recently, Fyfe[27] has observed several similar dienones generated during the bromination of 2,6-dialkylphenols in acetic acid using stopped-flow nmr techniques.

Cyclohexadienones can exist in two forms, the para-dienone, generated by bromine attack at the para position of a phenol, and the ortho dienone produced by ortho attack.



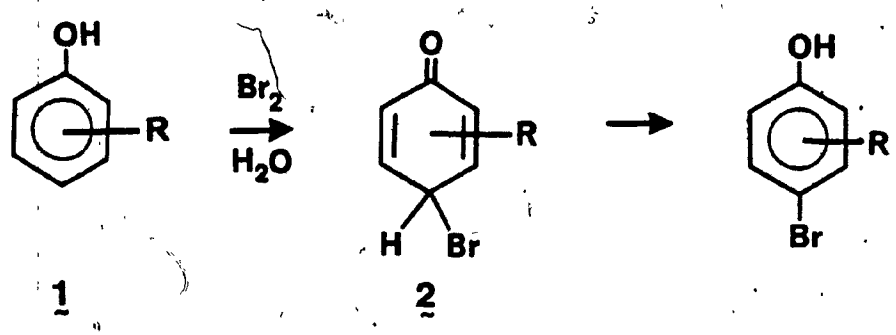
p-dienone



o-dienone

Of the two types, the ortho dienones are much more labile[28,29] and they have eluded detection during the bromination reactions.

Recently this laboratory has detected the formation of p-cyclohexadienone intermediates during the aqueous bromination of a variety of phenols.[28,29] Using stopped-flow ultraviolet absorption spectroscopy as the mode of detection, numerous mono and disubstituted alkyl 2,5-cyclohexadienones were discovered and their enolization to the p-bromo product was studied.



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Scheme 3 Enolization of 2,5-Cyclohexadienones

The first order rate constants corresponding to the intermediate breakdown were found to be independent of the initial concentrations of the substrate phenol, bromine and bromide ion, signifying that dienone formation is reversible. The observed rate constants, corresponding to a first-order enolization, were found to vary with pH to a minimal extent over a small range.

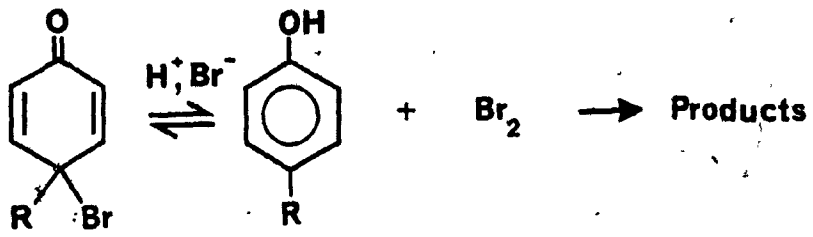
The cyclohexadienone intermediates undergo enolization between pH 0-6 via acid-catalysed and water-catalysed

mechanisms. In addition, they exhibit general acid and general base catalysis in the presence of buffers.[28,29]

Ipso-cyclohexadienones[30]

If the substrate phenol possesses an alkyl substituent at the para position, a dienone may be detected during the aqueous bromination which is termed an "ipso-dienone" since it results from ipso attack.

Following this laboratory's work with respect to the 2,5-cyclohexadienones, we focussed our attention on the possibility of observing the ipso-dienones formed by various p-alkylphenols under aqueous bromination conditions.[30] These intermediates cannot enolize but undergo decomposition by debromination.[31]



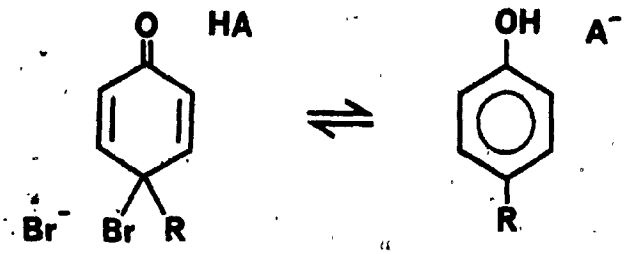
Scheme 4 Debromination of Ipso-dienones

Their formation by ipso bromine attack is responsible for 10% of the initial consumption of molecular bromine. After the initial rapid consumption of bromine, there is a slower decrease in absorbance near 250nm which is attributed to the first-order decay of the ipso-dienone. This decomposition of the intermediate has been found to be

catalysed by both H^+ and Br^- but the rate of intermediate decay is not particularly sensitive to the nature of the 4-alkyl substituent.

The proposed mechanism involves the debromination back to substrate and molecular bromine where the bromine is then repartitioned between ortho attack (90%) and ipso attack (10%) eventually leading to the ortho brominated product.

Under buffer conditions, it was also found that the dienone obtained from p-cresol demonstrates general acid catalysis. This was attributed to the mechanism shown below.



Scheme 5 Buffer Catalysis of Debromination Reaction

The Bronsted coefficient α, determined to be 0.27, describes a small but significant amount of general acid (HA) bond rupture at the transition state.

Objectives

Following on from our earlier work on anisole bromination,[20,21] the objective of the present study was to investigate the effect that α-cyclodextrin has on the aqueous bromination kinetics of phenol, various substituted phenols and their corresponding anions. Although we were confident that we would see catalytic or inhibitory effects, it was not known to what extent the electronic or steric effects of a given substituent might influence catalysis. By varying the type and position of the substituent, it was hoped that a more definite picture of the catalytic pathway involving α-cyclodextrin might be arrived at. Where necessary, the dissociation constants of the substrate-cyclodextrin complexes would be determined by appropriate methods.

In the case of reactions involving phenoxide ions, special attention was paid to the magnitude of the catalytic rate constants since these are normally diffusion-controlled.[25] The possibility of an enhanced contribution to the bromination reaction by the tribromide ion was also considered.

Since the substrates involved in the present study may generate either cyclohexadienones or the ipso-dienones during bromination, part of this investigation dealt with the effect of α-cyclodextrin on the enolization of 2,5-cyclohexadienones and the debromination of ipso-dienones in aqueous solution. It was hoped that this would provide

information about the inclusion of such compounds and reveal details of the catalysis. Furthermore, from the debromination reaction, additional insight into the (reverse) bromination reaction might be obtained.

Results

Using quantitative UV spectral studies and stopped-flow measurements, we have analysed the effect α-cyclodextrin has on the aqueous bromination kinetics of a variety of phenols. The present study also includes studies of the decomposition of intermediate 2,5-cyclohexadienones and ipso-dienones in the presence of α-cyclodextrin.

Our previous study of the kinetics of bromination of anisole and p-methylanisole in the presence of α-cyclodextrin[20,21] showed that the complexity of the catalytic reaction arises from the formation of several inclusion complexes. In order to better understand the current presentation, a portion of this section will highlight the equilibria discovered earlier[20] and which are pertinent to this study.

Equilibria

For reasons previously outlined,[32] it is useful to employ an aqueous medium containing an excess of bromide ion when studying bromination reactions. This being the case in the present study, one must first consider the equilibrium forming the tribromide ion:

$$Br_3^- \underset{}{\overset{K}{\rightleftharpoons}} Br_2 + Br^-$$

$$K = \frac{(Br_2)(Br^-)}{(Br_3^-)} = 0.0562M \quad (23)$$

For an excess of Br^- over Br_2, the fraction of free bromine

may be defined as:

$$f_B = \frac{K}{(K+[Br^-])} \qquad 1$$

This equilibrium, however, is substantially effected by the presence of α-cyclodextrin. Using quantitative UV spectral analysis and an extensive literature search, it was discovered that all three species involved in the above equilibrium form inclusion complexes with α-cyclodextrin.[20,21]

Wojcik and Rohrbach determined the dissociation constant, K_1, of the complex formed between α-cyclodextrin and the bromide ion[9] to be 0.286M. Although this value indicates weak binding, given the high bromide ion concentrations used, this equilibrium must be considered due to its effect on the amount of free cyclodextrin available for additional complexations.

Bromine has been found to form a stronger inclusion complex.[16,34] Under our experimental conditions where $(Br_2) < 50uM$, this complexation does not significantly effect the concentration of α-cyclodextrin but it does contribute to the reduction in the free bromine concentration.

$$]Br_2[\underset{}{\overset{K_B}{\rightleftharpoons}} Br_2 + CD$$

$$K_B = \frac{[Br_2][CD]}{[Br_2]_c} = 2.1mM \qquad (16)$$

The most significant complexation involving α-cyclodextrin was determined to be that involving the tribromide ion.[20] Using quantitative UV spectrophotometric methods modelled after those of Hildebrand and Benesi,[35] the inclusion complex dissociation constant was measured:

$$]Br_3^-[\underset{}{\overset{K_T}{\rightleftharpoons}} Br_3^- + CD$$

$$K_T = \frac{[Br_3^-][CD]}{[Br_3^-]_c} = 0.17mM \qquad (20,21)$$

The low value of K_T indicates ten-fold stronger binding than that of bromine and this complexation is the major factor in determining the free bromine concentration under the conditions of our kinetic experiments.

These complexations of bromine and tribromide ion manifest themselves as a reduction in the free bromine in solution. For total bromine,

$$[Br_2]_t = [Br_2]+[Br_3^-]+[Br_2]_c+[Br_3^-]_c \qquad 2$$

where the subscript c indicates complexed species, the previously defined fraction of free bromine f_B, must be modified to:

$$f_B = \frac{KK_BK_T}{K_BK_T(K+[Br^-])+[CD](KK_T+K_B[Br^-])} \qquad 3$$

Under the bromide ion concentrations generally used in this study, the term $K_B(Br^-)$ is much larger than KK_T and

so the demoninator takes an abbreviated form and f_B becomes

$$f_B = \frac{KK_T}{(K_T(K+[Br^-])+[Br^-][CD])} \qquad 4$$

As previously noted, substrate inclusion within the cyclodextrin cavity may be monitored spectrophotometrically where, depending on the extent and strength of binding, large changes in absorption and shifts in wavelength may occur.

$$]S[\overset{K_s}{\rightleftharpoons} S + CD$$

The determination of K_s, the substrate-cyclodextrin dissociation constant, used the Hildebrand-Benesi relationship[35] correlating the effect of α-cyclodextrin with

$$\frac{[S]}{(A - A_0)} = \frac{K_s}{\Delta\varepsilon[CD]} + \frac{1}{\Delta\varepsilon} \qquad 5$$

the change in observed absorption. The term $\Delta\varepsilon$ is the change in extinction coefficient due to complexation.

For certain of the compounds studied, the change in absorption due to complexation was extremely small. In cases of this nature, it was useful to employ a Eadie-Hofstée method of analysis. By correcting for the

known complexations of Br^-, Br_2 and Br_3^- the bromination kinetics data was analysed and K_s determined. This method will be discussed further when analysing the kinetic results.

The dissociation constants for the various substrate inclusion complexes involved in this study are summarized in Table I. The extent to which inclusion occurs varies markedly. 4-Bromophenol shows the strongest binding with a factor of sixty over the weakest bound substrate, p-cresol. Initial inspection suggests the absence of any direct correlation between the electronic or steric nature of substitution with the substrates ability to bind.

Although many of the substituted phenoxide ions have been shown to undergo cyclodextrin encapsulation in previous studies, the dominant form of the substrate involved in complexation is the parent phenol within the pH range of our kinetic studies. In certain cases, the bromination reaction occurs via the ionized form of the phenol but this form is present in such minute quantities that its encapsulation is neglible in terms of reducing the amount of free substrate.

Table I: Substrate Inclusion Complex Dissociation Constants for Phenol and Derivatives (25°C)

Phenol	No.	K_S, mM	Reference
H	1a	50	16
4-Me	1b	83	16
2-Me	1c	4.3	b,c
2,6-diMe	1d	26	b
4-t-Bu	1e	12	10
4-NO_2	1f	4.4	a
2-NO_2	1g	38	a
3-NO_2	1h	6.6	d
2-Br	1i	52	a
4-Br	1j	1.4	a
4-CN	1k	7.0	36
4-COOEt	1l	4.8	b

a. Determined spectrophotometrically

b. From Eadie-Hofstee analysis

c. 1.0M KBr

d. Interpolated value from data at higher and lower temperatures.[37]

Reaction Kinetics: The Phenols

As stated previously, the aqueous bromination kinetics of phenol and various substituted phenols have been examined extensively[23-25,38] and their repective pH-rate profiles have been well-documented. These studies have shown that at low pH, the reactive species is the parent phenol and not the ionized form. Reaction via the anion is involved at higher pHs. In addition, the reactions monitored in previous and the current study exhibit overall second-order reaction kinetics: first order in both reactants.

The present research on the effects of α-cyclodextrin on the aqueous bromination of phenols and phenoxide ions again shows the complex rate behaviour first found for anisole.[20,21] In the uncatalysed reaction, the bromination kinetics are governed by the rate expression:

$$PhOH + Br_2 \xrightarrow{k_2} \text{products}$$

$$\text{rate} = k_2^{app}[S][Br_2]_t = k_2[S][Br_2] \qquad 6$$

therefore:

$$k_2^{app} = k_2 f_B \qquad 7$$

where $f_B = (Br_2)/(Br_2)_t$ is the fraction of free bromine. The observed bromination rate constant may be expressed as $k_2^{obs} = k_2^{app}/f_B$. Our result for the uncatalysed phenol bromination at 0.1M KBr shows good agreement with the results of Paventi[25] where $k_2^{obs} = 4.5 \times 10^5 M^{-1}s^{-1}$ (1M KBr).

In the presence of α-cyclodextrin, however, the apparent second-order rate constant k_2^{app} for phenol shows a variation due, in part, to the additional complexations involving bromine species. Here, f_B must take account of these encapsulations. In addition, since phenol complexation is known to occur[16] the mathematical treatment of the rate expression must be redefined so as to consider substrate encapsulation. Since:

$$f_s = [S]/[S]_t \quad ; \quad [S]_t = [S]+[S]_c$$

$$\underline{\text{or}} \quad f_s = \frac{K_s}{K_s+[CD]} \qquad 8$$

then:

$$k_2^{app} = k_2 f_s f_B \qquad 9$$

This rate expression now accounts for all the known complexations. Table II shows the apparent second-order rate constants obtained for the bromination of phenol as a function of α-cyclodextrin concentration under 0.1M and 0.05M KBr conditions (ionic strength maintained at 0.1u, see experimental). In both examples, the rate shows slight acceleration with increasing catalyst concentration. If bromination proceeded solely via both free reactants, k_2^{app} should decrease dramatically with increasing cyclodextrin concentration. Figure 2 shows this situation, where the calculated second-order rate constant is graphically compared to the observed k_2^{app} as a function of cyclodextrin

Table II: Apparent Second Order Bromination Rate Constant for the Bromination of Phenol as a Function of α-Cyclodextrin Concentration (25°C)

	(CD), mM	$k_2^{app} \times 10^{-5} M^{-1} s^{-1}$
(a) 0.1M KBr, pH= 1.84	0	1.48
	0.10	1.81
	0.25	2.28
	0.50	2.59
	1.00	2.81
	2.00	2.98
	5.00	2.89
(b) 0.05M KBr, pH= 2.07	0	1.82
	0.10	2.67
	0.25	3.34
	0.50	4.02
	1.00	4.61
	2.00	5.14
	5.00	5.14

In both cases, (Sub)= 0.10mM; (Br_2)= 0.01mM

concentration. It is quite clear that there exists an additional phenomenon previously unaccounted for. The discrepancy between the observed and calculated rate constants is of the order of 37.2 at the maximum cyclodextrin concentration. In the calculated case, a rapid decline in rate occurs at low α-cyclodextrin concentrations and eventually levels off due to saturation of the complexation equilibrium.

The observed values of k_2^{app} exhibit quite the opposite picture where the initial rate shows slight acceleration and subsequent rate saturation at higher α-cyclodextrin concentrations. With rate acceleration (and not inhibition) being the case, it appears that there exists a bromination pathway involving α-cyclodextrin. The presence of such a pathway is consistent with the results obtained for the aqueous brominaton of anisole.[20,21]

The second order pathway present may be represented as one of the following:

$$]S[+ Br_2 \longrightarrow A$$

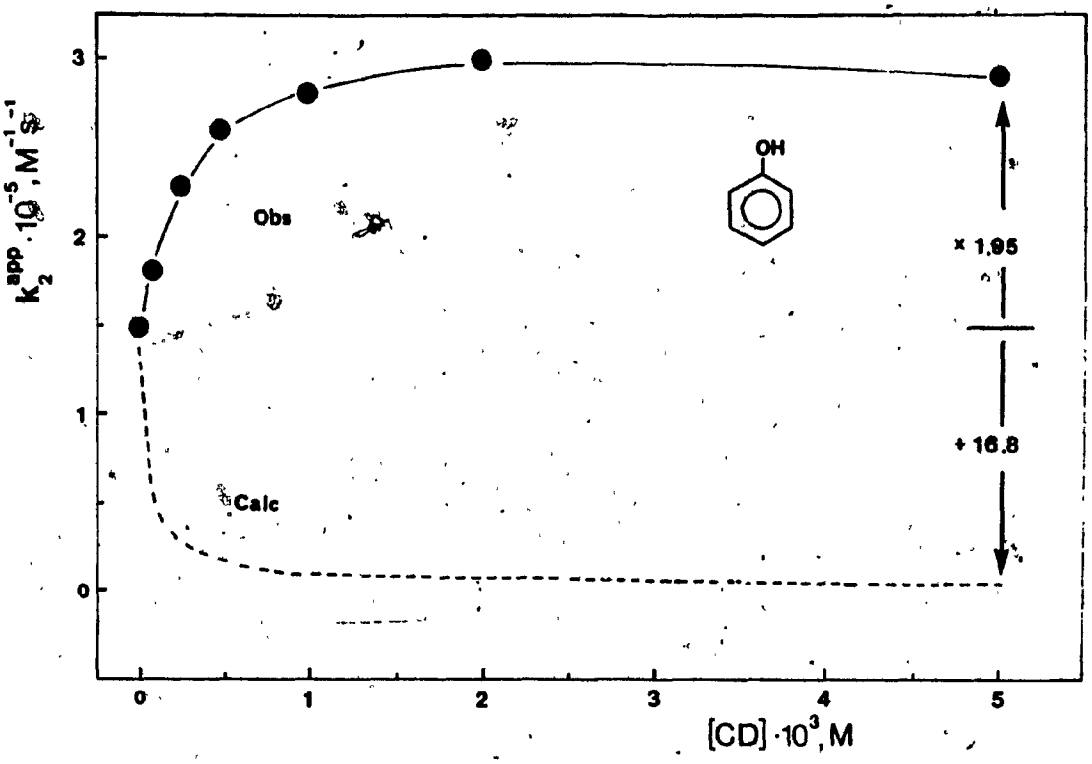
$$S +]Br_2[\longrightarrow B$$

$$]S \cdot Br_2[\longrightarrow C$$

$$S +]Br_3^-[\longrightarrow D$$

Scheme 6

Figure 2: Calculated* and Experimental Apparent Second-order Rate Constants for Phenol (1a) as a Function of α-Cyclodextrin Concentration



Conditions: 0.1M KBr, pH= 1.84

* Calculation based on reaction of free substrate and free bromine (eq. 9)

Case A represents the attack of free bromine with complexed substrate. Conversely, case B is for the reaction of free substrate with encapsulated bromine. Case C indicates reaction taking place within a distinct ternary complex of cyclodextrin, substrate and bromine. Case D indicates the possibility of reaction involving encapsulated tribromide ion, which is a major form of the total bromine.

If the reaction proceeds via case A:

$$k_2^{app} = k_2 f_s f_B + k_2^c (1-f_s) f_B \qquad 10$$

where $(1-f_s)$ is the fraction of substrate in the complexed form. This expression may be rearranged to give the linear form:[20,21]

$$\frac{k_2^{corr}}{f_B} = k_2 + \frac{k_2^c}{K_s}[CD] \qquad 11$$

where $k_2^{corr} = k_2^{app}/f_s$. For case B, the corresponding expression is:[20,21]

$$\frac{k_2^{corr}}{f_B} = k_2 + \frac{k_2^c}{K_B}[CD] \qquad 12$$

Although both representations are correct, they differ in the numerical value of the catalytic rate constant k_2^c due to the complexation dissociation constants present in

in each denominator. A similar expression applies to case C.

Experiments involving substrate and bromide ion dependence in the absence of and at a constant α-cyclodextrin concentration, as shown in Table III, suggest that the reaction is first order in substrate, bromine and α-cyclodextrin. As emphasized later, the possibility of reactions of higher order in cyclodextrin is not present. In addition, the absence of rate variation with changing bromide ion concentration does not support the involvement of the tribromide ion as a catalytic bromination species (case D).

In order to rule out the possibility of reaction via a hypobromite of α-cyclodextrin, pH dependence studies at 5mM cyclodextrin concentrations were also conducted (Table III). This experiment is justifiable in that the chlorination of anisole was found to proceed via a hypochlorite ester of α-cyclodextrin in Breslow's study.[16,34] In the current study, there does not appear to be a contribution via this type of pathway since the rate should increase with pH. Since the catalytic pathways A, B, and C are kinetically indistinguishable, the slopes and intercepts for the bromination of phenol and subsequent studies will be reported as their numerical values with discussion of the significance of the results reserved for later.

Figure 3 shows the results obtained from the aqueous bromination of phenol at 0.1M KBr as a function of α-cyclo-

Table III: pH, Substrate and Bromide Ion Dependence at Fixed Cyclodextrin Concentrations

(CD),mM	pH	$k_2^{app} \times 10^{-5}$
0	1.17	1.49
	2.08	1.53
	2.92	1.64
5.00	1.14	3.19
	2.08	3.39
	2.89	3.67

(CD),mM	(Sub),mM	
5.00	0.10	2.97
	0.20	2.79

(CD),mM	(Br^-),M	$k_2^{corr}/f_B \times 10^{-7}$
5.00	0.10	1.68
	0.075	1.31
	0.05	1.72
	0.025	1.27

All cases: (Br_2)= 0.01mM, (Sub)= 0.1mM (except Substrate dependence), 0.1M KBr (except 3)

pH= 2.08 (case 2), case 3= 0.01N HCl

Units for k_2 (and corrected k_2) are $M^{-1}s^{-1}$.

dextrin concentration treated according to:

$$\frac{k_2^{corr}}{f_B} = \text{int} + \text{slope}[CD] \qquad 13$$

with the resulting linear plot showing good correlation ($r = 0.99986$), the slope being $3.52 \times 10^9 M^{-2}s^{-1}$. The good linearity indicates that one molecule of α-cyclodextrin is involved in the transition state of the catalysed bromination pathway. The intercept, which describes the uncatalysed reaction, may not give a truly accurate value of k_2 therefore the experimentally obtained rate constant at zero cyclodextrin concentration will be cited in future text.

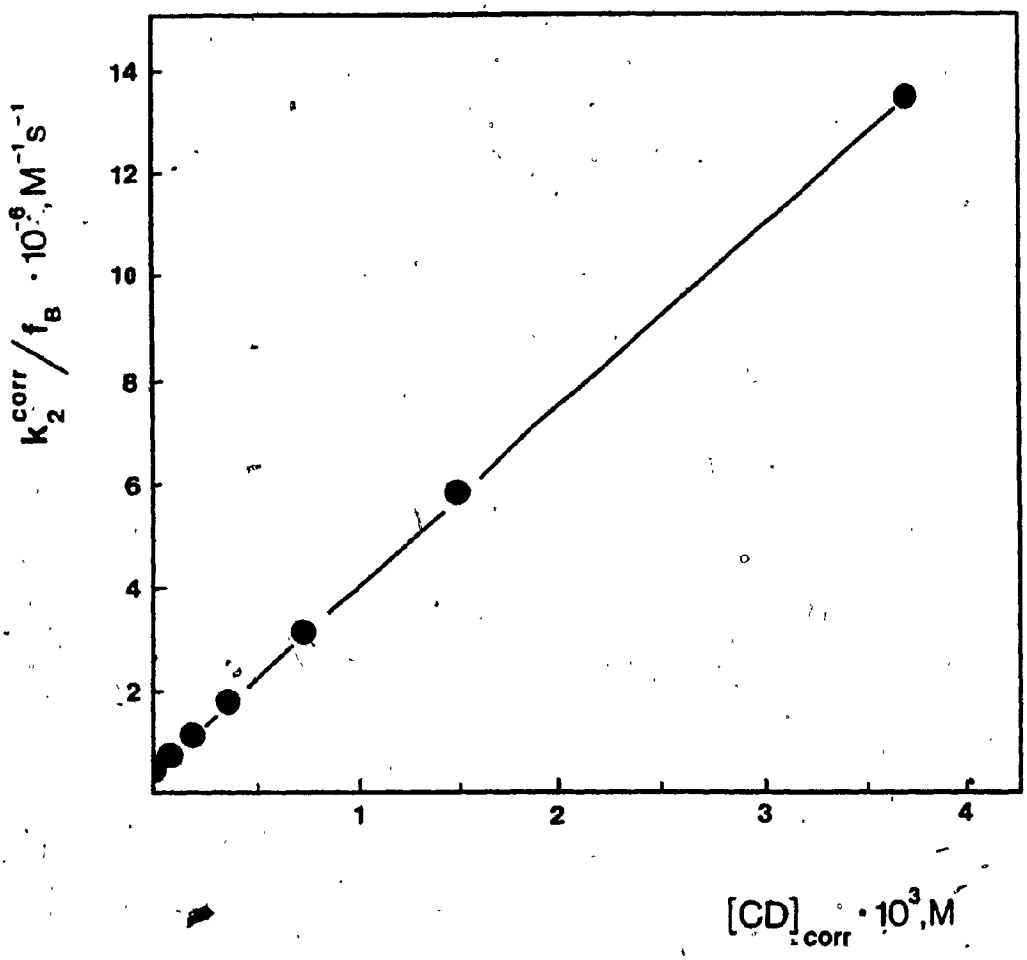
Based on the successful results obtained for phenol, a series of mono and di-substituted phenols were studied in the same manner. These substrates, 1b-1e, all undergo complexation with the cyclodextrin however, the extent to which binding occurs is relatively weak. In certain cases, UV absorption spectroscopy could not be used to determine K_s due to the extremely small changes in absorption with increasing cyclodextrin concentration. This being the case, a manipulation of the rate expression was used to give a calculated result for K_s, based on the kinetic results. This yields a modified Eadie-Hofstée formula, which may be expressed as:

$$(k_2^* - k_2^u) = -\frac{(k_2^* - k_2^u)K_s}{[CD]} + (k_2^c - k_2^u) \qquad 14$$

where,

$$k_2^* = k_2^{app}/f_B$$

Figure 3: k_2^{corr}/f_B as a Function of Cyclodextrin Concentration (0.1M KBr, pH= 1.84)



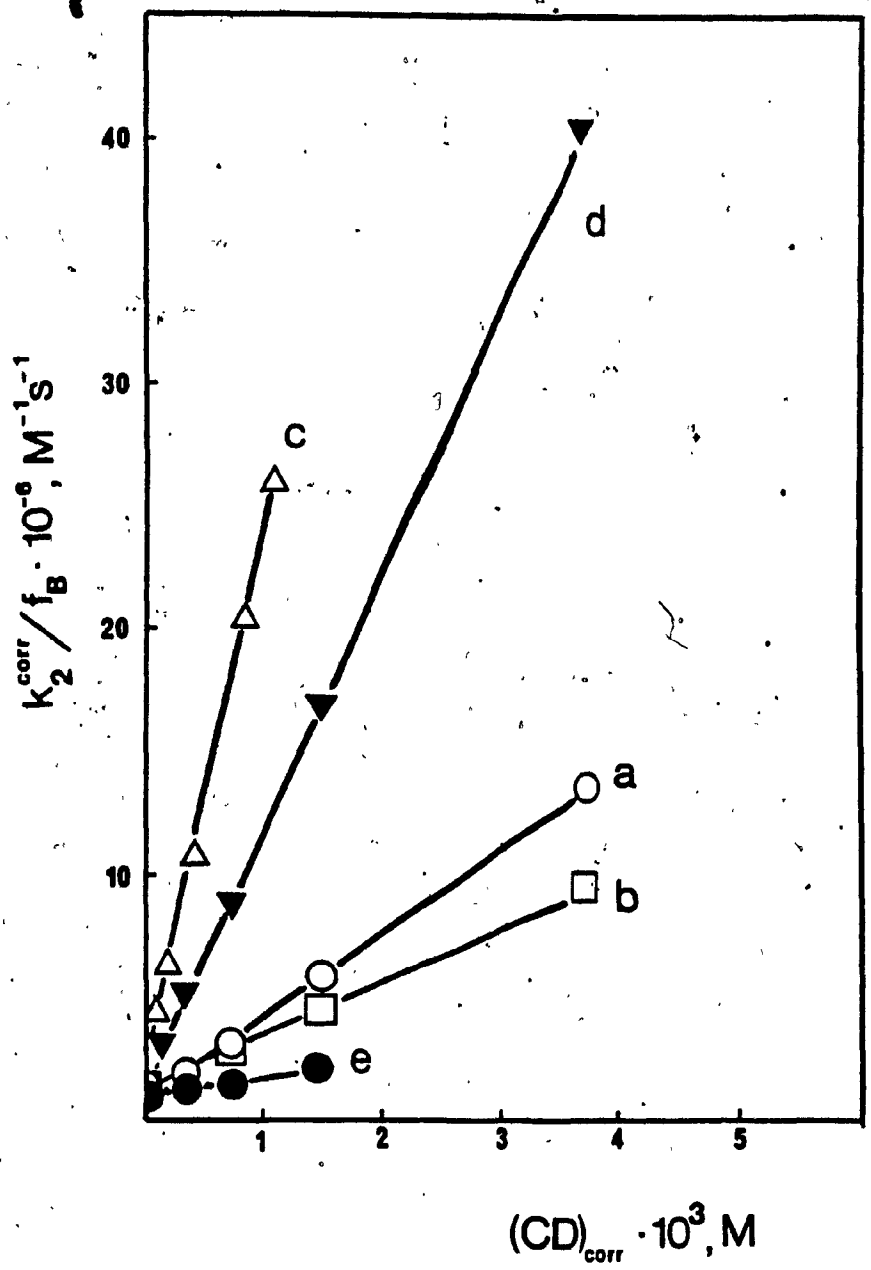
Additional methods including a Lineweaver-Burke approach and non-linear fitting techniques[39] were also tried to obtain a value for K_s. However, the Eadie method was chosen based on its statistical superiority.[42] This expression was used to determine the K_s for 1c as well as additional substituted phenols (see Table I).

Figure 4 shows the results obtained for the bromination of phenols 1a-1e as treated by equation 13. The plots all show good linearity, indicating the involvement of one molecule of α-cyclodextrin in the reaction. Examination of the plots shows the variation in the catalytic rates between the different substrates, with 1c showing the largest catalytic rate acceleration.

Phenols possessing electron-withdrawing substituents have been shown to exhibit bromination via their parent forms at low pH values.[23-25,38] As was the case with compounds 1a-1e, kinetic evaluation of the data for compounds 1i-1l suggests the presence of a catalytic pathway involving cyclodextrin.

Tables IV summarize the results for phenol, the alkyl-substituted phenols 1a-1e and compounds 1i-1l in terms of their uncatalysed rate constants and slopes. Just as for 1a-1e, good linearity was found for the plots of k_2^{corr}/f_B versus (CD) (eqn. 13) for the substrates 1i-1l ($r = .9995$).

Figure 4: k_2^{corr}/f_B as a Function of Cyclodextrin Concentration[a] for Phenols 1a-1e



a. All representations (excluding 1c= 1.0M KBr) at 0.1M KBr. Data for Figure 4 taken from Table XII, Appendix

Table IV: Resultant Values for k_2 and Slopes for Substrates 1a-1e as Treated by Equation 13 (25°C)

Substrate	$k_2^{un} x10^{-5}$	Slope $x10^{-9}$
1a	4.11	3.52
	3.43(0.05M)	3.36
1b	6.59	2.36
	5.90(0.05M)	2.01
1c	16.2 (1.0M)	21.7
1d	12.0	10.7
1e	5.86	0.843
1i	0.101	0.0672
1j	0.0389	0.00854
1l	0.0155	0.00335
1k	0.00155	0.000441

1. Conditions are 0.1M KBr unless specified. Correlation coefficients were >.9992, mostly .9995. Units of $k_2=M^{-1}s^{-1}$

2. Data for substrates 1i-1l from Table XIII, Appendix

The Phenoxides

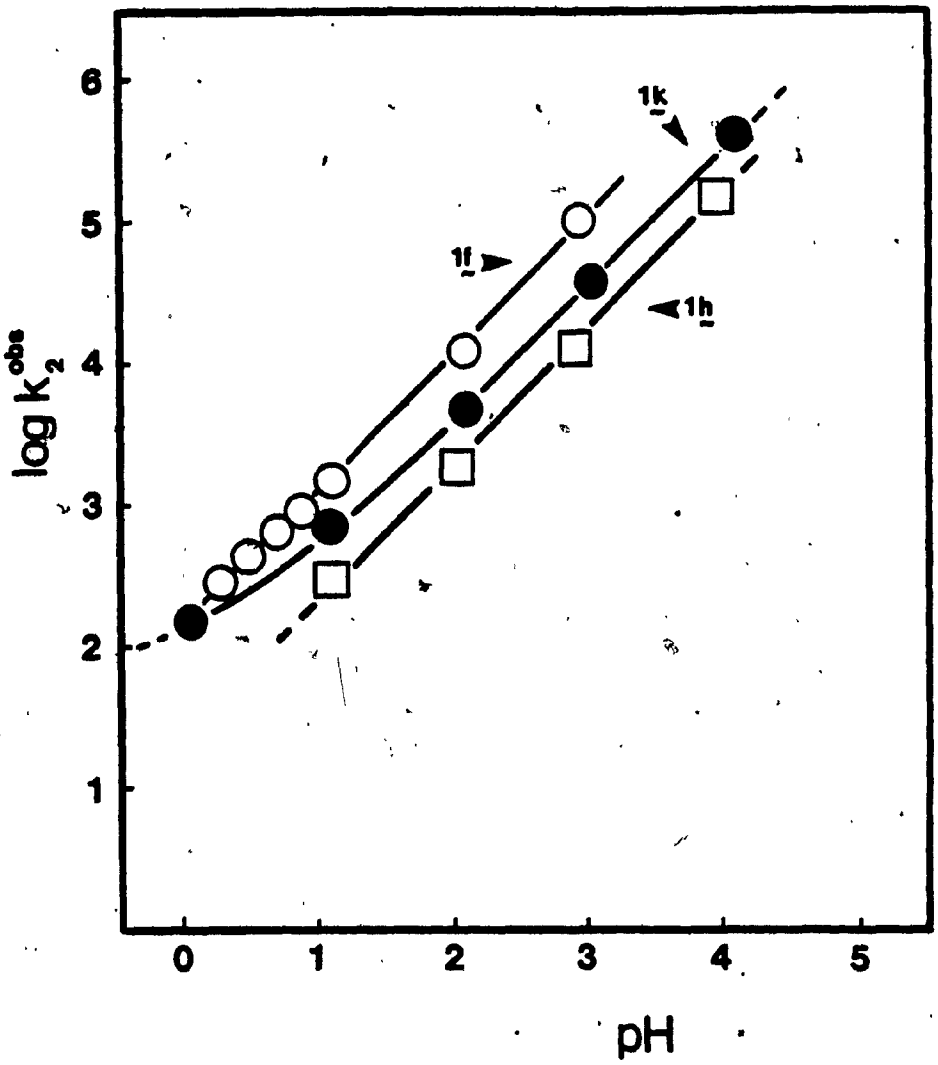
The bromination of a series of phenols bearing electron-withdrawing substituents have been studied between pH 1-5, at first in the absence of α-cyclodextrin. Their pH-rate profiles show that the reaction proceeds via their respective phenoxide ions.

Figure 5 shows the pH-rate profiles for the brominaton of the three nitro isomers of phenol (1f-1h) and p-cyanophenol, 1k. As expected from earlier work,[23-25,38] all four compounds exhibit pH dependence at pH > 1 whereby reaction proceeds via the respective phenoxides. Compound 1k, however, shows a levelling off at pH < 1 suggesting that under highly acidic conditions, the parent phenol is the form which undergoes bromination (see earlier).

As mentioned earlier, all the substrates exhibiting bromination via their anions have been found to undergo complexation with α-cyclodextrin. In certain instances, complexation of phenolate anions has also been shown.[12]

As was the case with phenol and the alkyl-substituted phenols, the bromination of substrates 1f-1l all exhibit complex rate behaviour in the presence of α-cyclodextrin. In addition, a catalytic pathway involving α-cyclodextrin was present in all cases. Data analysis revealed that treatment of the bromination reaction in the presence of α-cyclodextrin follows that derived for the phenols ie. equation 13, however in determining the magnitudes of the catalysed and uncatalysed rate constants, the dependence of

Figure 5: pH-Rate Profiles for the Aqueous Bromination of Phenols 1f-1h, 1k



All experiments under 0.1M KBr conditions

(Sub)= 0.5mM, (Br_2)= 0.05mM

The data for 1g are virtually coincidental with that of 1f. They have, therefore, been omitted for clarity.

the bromination rate on pH must be taken into account.

Table XIV (see Appendix) shows the results of the bromination of p-nitrophenol (1f) as a function of α-cyclodextrin under different conditions of pH and bromide ion concentration. Each reaction exhibits a progressive decline in k_2^{app} with increasing cyclodextrin concentration.

In cases where the bromination reaction proceeds via the anion form, data analysis must account for the pH-dependence of the phenoxide concentration. Since

$$PhO^- + Br_2 \xrightarrow{k_2} \text{products}$$

and the catalytic pathway proceeds via a form involving α-cyclodextrin, then the expression for k_2^{corr}/f_B becomes

$$\frac{k_2^{corr}}{f_B} = \frac{K_a}{[H^+]}(\text{int} + \text{slope} \cdot [CD]) \qquad 15$$

since both the uncatalysed rate k_2 and k_2^c depend on the ratio of anion/phenol present. This ratio is equal to $K_a/(H^+)$ where K_a is the phenol dissociation constant.

Data analysis for the p-nitrophenol experiments according to equation 15 shows good linearity which supports the involvement of α-cyclodextrin in a rate catalysing pathway. As seen in Table V, there appears good correlation between values of k_2 and slope at different pH and bromide ion

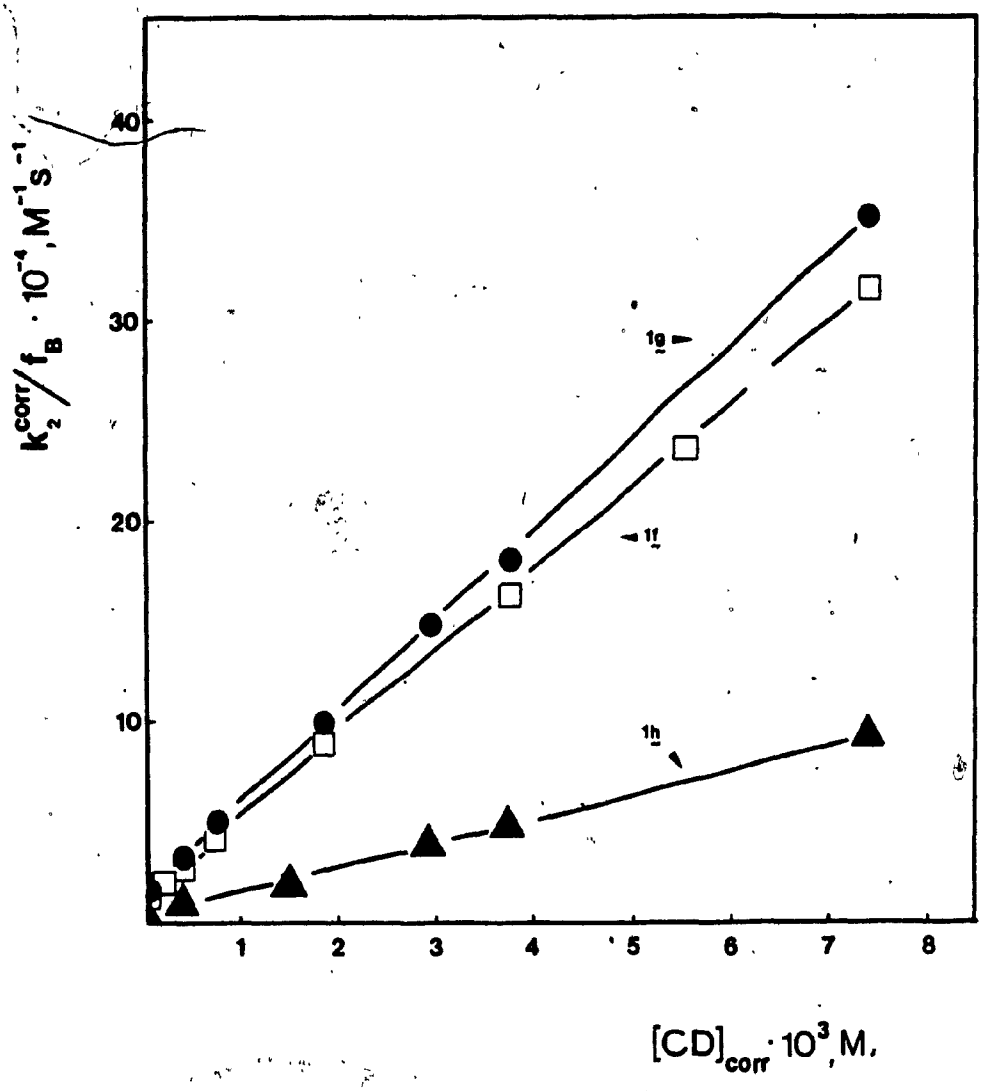
concentrations.

Bromination experiments were conducted on a series of substituted phenols proceeding by their ionized forms with α-cyclodextrin at various pH values. These experiments included phenols possessing substituents at various positions. Figure 6 shows the results obtained for the three nitro isomers of phenol (1f-1h) plotted according to equation 15. As seen earlier with phenols, an additional rate catalysing pathway compensates for the rate reductions due to the various complexations involved. Each isomer shows varying degrees of catalysis, yet all the plots show excellent linearity. Additional experiments involving o-bromo, p-bromo and p-cyanophenol (1i-1k) showed similar rate behaviour and analysis of the data again followed from equation 15.

Table V summarizes the analysed results obtained for the bromination of phenols 1f-1k in the presence of cyclodextrin according to the values k_2 and slopes (where $m = k_2^C/X$). The ratio $K_a/(H^+)$ has been accounted for in the analysis. All substrates show uncatalysed rate constants approaching diffusion-controlled limits. Of particular interest are the magnitudes obtained for k_2^C/X.

In order to ascertain whether a bromination pathway involving the tribromide ion was involved, bromide ion dependence studies were performed on 1h, m-nitrophenol, which shows the greatest catalysis with cyclodextrin. Bromide ion dependence has been found by Bell and Rawlinson[22] in

Figure 6: k_2^{corr}/f_B vs. Cyclodextrin Concentration for Reaction Proceeding Via the Anions of Phenols 1f-1h



Data from Tables XIV and XVI of the Appendix.

Results for 1f at 0.1M KBr, pH= 2.07

Table V: Resultant Values for k_2 and Slope for Reaction Proceeding Via Anions 1f-1k as Treated by Equation 15 (25°C)

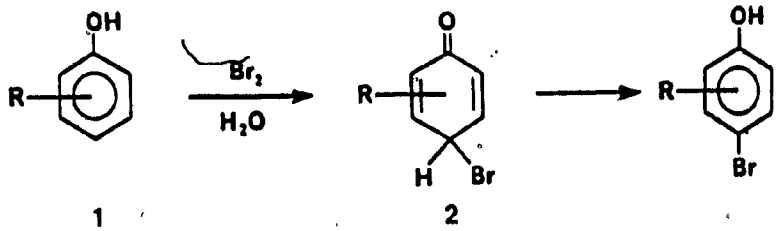
Substrate	pKa[1]	$k_2^{un} \times 10^{-9}$	Slope= $k_2^c/X \times 10^{-12}$
1f	7.14	1.18	7.71
		1.08	7.62
		1.02	7.81
		1.07	6.57
1g	7.23	1.66	5.71
1h	8.35	3.13	28.1
1i	8.42	6.16	7.86
1j	9.36	11.6	19.8
1k	7.95	3.24	5.81

1. For treatment by eq. 15, r= 0.9996
2. All pKa values (except 1j) are taken from Jencks[40]. Thermodynamic pKa's have been corrected for ionic strength in data analysis.
3. 1j pKa from (25).
4. Results for substrate 1f at two pH's, two (Br^-).
5. Units of k_2, k_2^c= $M^{-1}s^{-1}$.

the bromination of m-nitrophenol via its anion consistent with a contribution from the reaction with the tribromide ion. Our experiments, carried out at zero and 5mM cyclodextrin at bromide ion concentrations ranging from 0.025-0.1M KBr showed no significant contribution from the tribromide ion. An average value of k_2^{corr}/f_B was found to be $1.04 \times 10^4 M^{-1}s^{-1}$ (0.1N HCl). The fact that no bromide ion dependence was seen in the m-nitrophenol case will be an important consideration in the discussion as to the form of the catalytic pathway involved in the bromination of phenols in the presence of cyclodextrin.

The Cyclohexadienones

As mentioned earlier, transient 4-bromo-2,5-cyclohexadienones have been observed during the aqueous bromination of phenol and phenols possessing methyl groups at positions 2,3,5, and/or 6.[28,29] These intermediates are converted to products by an enolization mechanism.[29]



1 2

Scheme 7

Due to the effects of α-cyclodextrin on the bromination kinetics of the phenols studied, an investigation into the possibility of rate perturbation of the enolization process by α-cyclodextrin was initiated.

Kinetic experiments were conducted on a series of phenols capable of generating the 4-bromo-2,5-cyclohexadienone using the stopped-flow method and optical conditions previously described.[28,29] All experiments were carried out under dilute acid conditions where the disappearance of the respective intermediates show pH-rate dependence.

Table VI summarizes the first-order rate constants obtained as a function of cyclodextrin concentration for the intermediate enolizations of phenols 1a, 1d, 1m and 1n.

Table VI: Rate of Enolization of Intermediates 2 as a Function of Cyclodextrin Concentration (25°C)

Cyclohexadienone	(CD), mM	k_1^{obs}, s^{-1}
2a, R= H	0	12.4
	0.25	13.1
	0.50	13.3
	1.0	13.3
	2.0	13.2
	4.0	12.5
	5.0	12.3
	10.0	11.1
2m, R= 3-Me	0	14.4
	0.50	15.2
	1.0	14.1
	2.0	13.8
	4.0	12.9
	5.0	13.3
	10.0	11.9
2n, R= 2,5-diMe	0	6.87
	0.50	6.67

Table VI continued

2n	1.0	6.51
	2.0	6.59
	4.0	6.46
	5.0	6.39
	10.0	6.25
2d, R= 2,6-diMe	0	0.427
	0.10	0.460
	0.25	0.466
	0.50	0.477
	1.0	0.482
	2.0	0.481
	4.0	0.467
	5.0	0.463
	10.0	0.441

All reactions have (Sub)=0.5mM; (Bromine)= 0.05mM

2a,m,d run where conditions were 0.01N HCl, 0.1M KBr

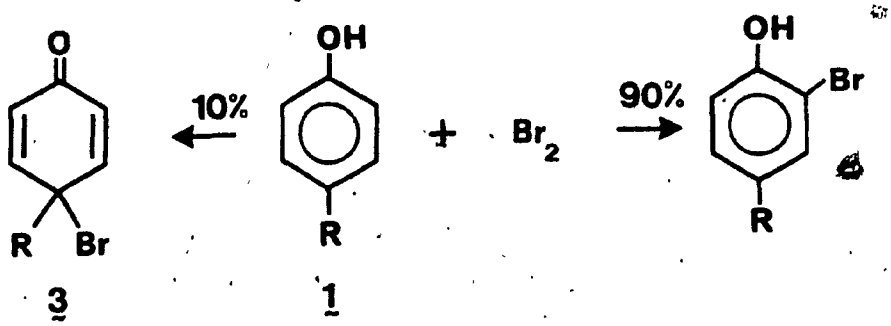
2n: 0.1N HCl, 1M KBr

Each of the transient intermediates 2a, m, n and 2d exhibit little change in enolization rate with increasing α-cyclodextrin concentration. This lack of rate perturbation may suggest that intermediate encapsulation is unfavourable. If the extent to which the intermediate penetrates the hydrophobic cavity is small, then the presence of a catalytic enolization pathway may not be kinetically evident.

The data show insufficient variation with increasing cyclodextrin concentration for successful analysis by an Eadie-Hofstée (or any other) treatment. Accordingly, this study was not pursued further.

The Ipso-dienones

The presence of a transient ipso-dienone during the aqueous bromination was first detected by this laboratory for the bromination of p-cresol.[28] Subsequently, several other such 4-alkyl-2,5-cyclohexadienones (3), derived from other p-alkylphenols, were detected and studied.[30,38]

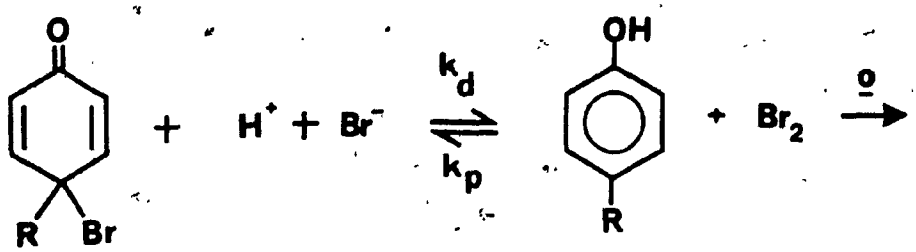


Scheme 8

The initial fast consumption of bromine is partitioned between ortho attack (~90%) and para (ipso) attack (~10%)[28,30]. However, the ipso-dienone represents a dead-end since it cannot enolize. Instead, it decomposes by debromination back to p-alkylphenol plus bromine. The bromine so produced is then repartitioned (~ 90:10) between ortho and para attack and so ultimately all of the bromine is converted to ortho product.[28,30,38]

The debromination reaction shows pH dependence and bromide ion dependence which can be explained by the pathway below and by treating the liberated bromine as a steady-state intermediate.[28,30,38]

Initial studies involving the debromination of the

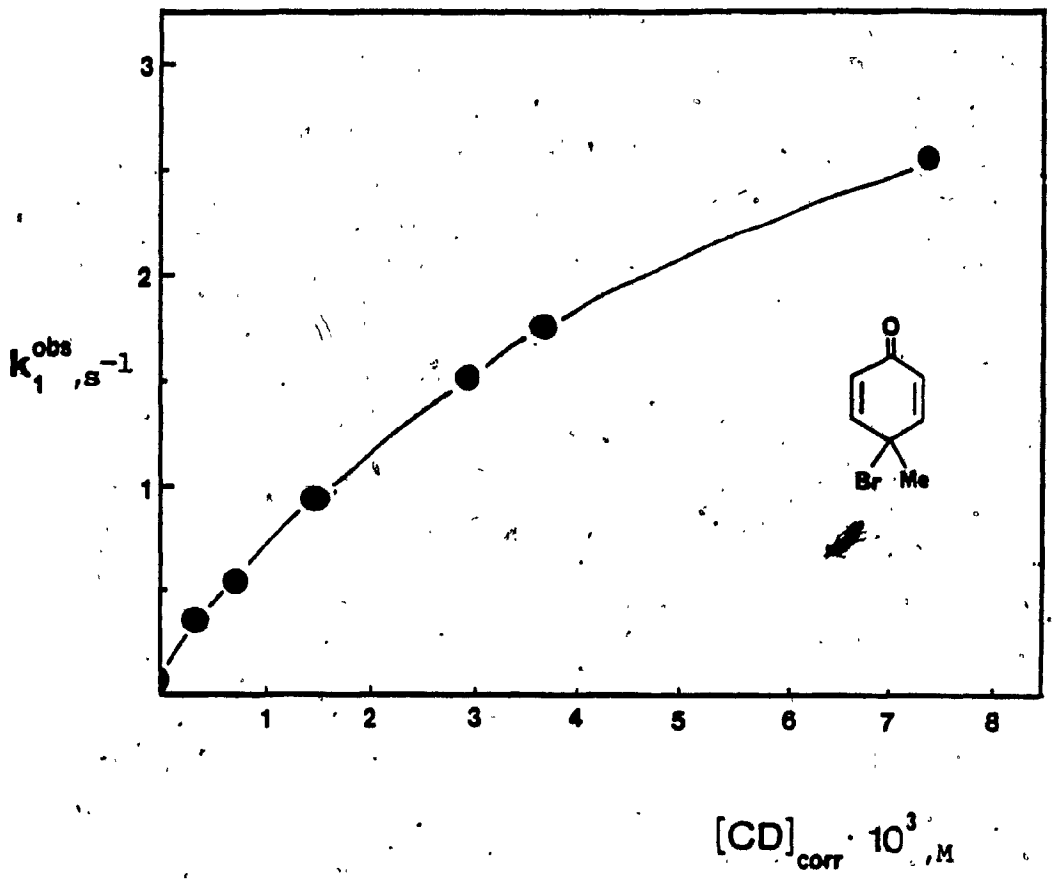


Scheme 9

ipso-dienone of p-cresol (1b) in the presence of α-cyclodextrin showed a remarkable rate acceleration. These reactions and those for all dienones studied were carried out under phenol trap conditions previously described.[30] Here, the presence of phenol essentially eliminates the back reaction (k_p) forming the ipso-dienone by "trapping" liberated bromine. Under these conditions, the forward reaction of ipso-dienone debromination becomes solely rate-limiting.

Figure 7 shows first-order rate constants obtained for the decomposition of the dienone 1b as a function of cyclodextrin (in aqueous 0.1M KBr and 0.05N HCl). A remarkable acceleration of the order of sixty five fold is observed which clearly indicates the presence of a cyclodextrin-catalysed pathway for debromination. This observation, coupled with the results obtained for the bromination of phenols in the presence of the cyclodextrin follow the theory of microscopic reversibility.[41] Here, since cyclodextrin effects the second-order bromination of p-cresol, it in turn must effect the debromination

Figure 7: First Order Debromination Rate for 1b (p-cresol) as a Function of Cyclodextrin Concentration



0.1M KBr, 0.05N HCl, Data from Table XVII, Appendix

reaction.

The debromination of ipso-dienones in the presence of α-cyclodextrin may be represented by an uncatalysed pathway (k_u) and a catalytic pathway involving either complexed dienone (I) intermediate or complexed bromide ion.

$$I + Br^- \xrightarrow{k_u}$$

and

or

$$\underline{a} \quad]I[+ Br^- \longrightarrow$$

$$\underline{b} \quad]I +]Br^-[\longrightarrow \qquad k_c$$

Scheme 10

Mathematical treatment of the above expression involves defining the fraction f_I which is the fraction of free intermediate. K_I is the dissociation constant of the ipso-dienone complex.

$$f_I = \frac{[I]}{[I]_t} = \frac{K_I}{(K_I+[CD])} \qquad 16$$

The rate expression, under cyclodextrin conditions is shown by:

$$k_{obs} = (k_u + k_c(1-f_I) \qquad 17$$

$$k_{obs} = (k_u + \frac{k_c}{K_1}[CD])f_I \qquad 18$$

Each representation differs from the other in the term defining the catalysed debromination pathway ie. which complexed reactant is involved in the catalysed process.

Several analysis techniques were considered for data treatment. By substituting for the term f_I in 17, then upon rearrangement, a non-linear expression is produced.

$$k_{obs} = \frac{k_u K_I + k_c[CD]}{(K_I + [CD])} \qquad 19$$

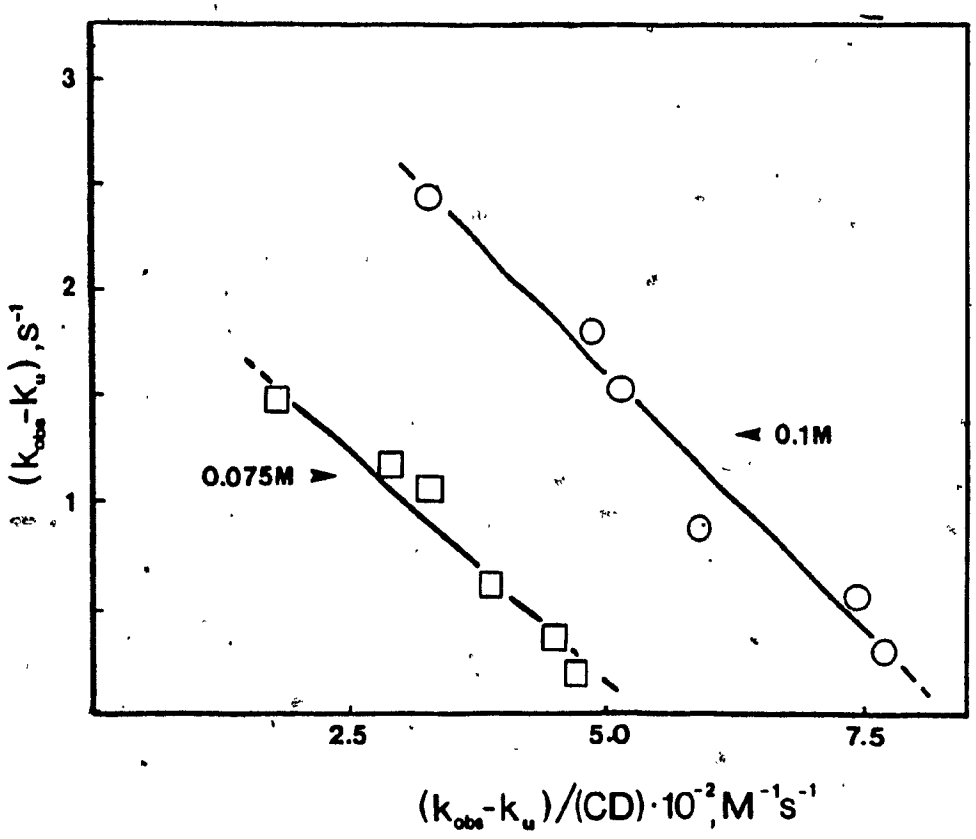
Alternatively, mathematical manipulation of 17 or 18 will give Lineweaver-Burke and Eadie-Hofstée treatments. The latter treatment (see Appendix for derivation) may be expressed as:

$$(k_{obs} - k_u) = -\frac{K_I(k_{obs} - k_u)}{[CD]} + int \qquad 20$$

The term defining the intercept includes the catalysed debromination rate constant, k_c. The magnitude of k_c will depend on which pathway is operative. The Eadie-Hofstée approach was chosen for its statistical superiority[42] in determining the parameters K_I and k_c.

Figure 8 shows the results obtained for the cyclodextrin-catalysed debromination of the ipso-dienone 1b at 0.1M and 0.075M KBr respectively. In all, four different bromide concentrations were analysed. It can be seen that

Figure 8: Eadie-Hofstée Treatment for 1b in α-Cyclodextrin at 0.1M and 0.075M KBr Concentrations



Conditions: 0.05N HCl, (Sub)= 0.2mM, (Br_2)=0.02mM (Phenol Trap), data from Table XVII, Appendix

both sets of data, as treated by 20, possess similar slopes which measures K_I for the intermediate-CD complex. A value $K_I \simeq 4.8$mM is obtained by this method indicating that binding of the ipso-dienone is quite strong. In addition, the intercept values vary in accordance with the bromide ion concentration. It can be concluded, therefore, that the catalysed pathway is bromide ion dependent, which agrees with the schemes presented above for this pathway.

Table VII summarizes the results obtained for the debromination of 1b at several bromide ion concentrations in terms of K_I and the intercept as treated by the Eadie-Hofstée method. It should be noted that the results show good agreement with both the Lineweaver-Burke and nonlinear fitting techniques.

Table VII: Bromide Ion Dependence Data According to eq. 20 for the Debromination of 1b in the Presence of α-Cyclodextrin (0.05N HCl)

(Br^-), M	K_I, mM	intercept
0.20	3.66	6.11
0.10	4.82	4.01
0.075	4.59	2.43
0.05	6.65	2.37

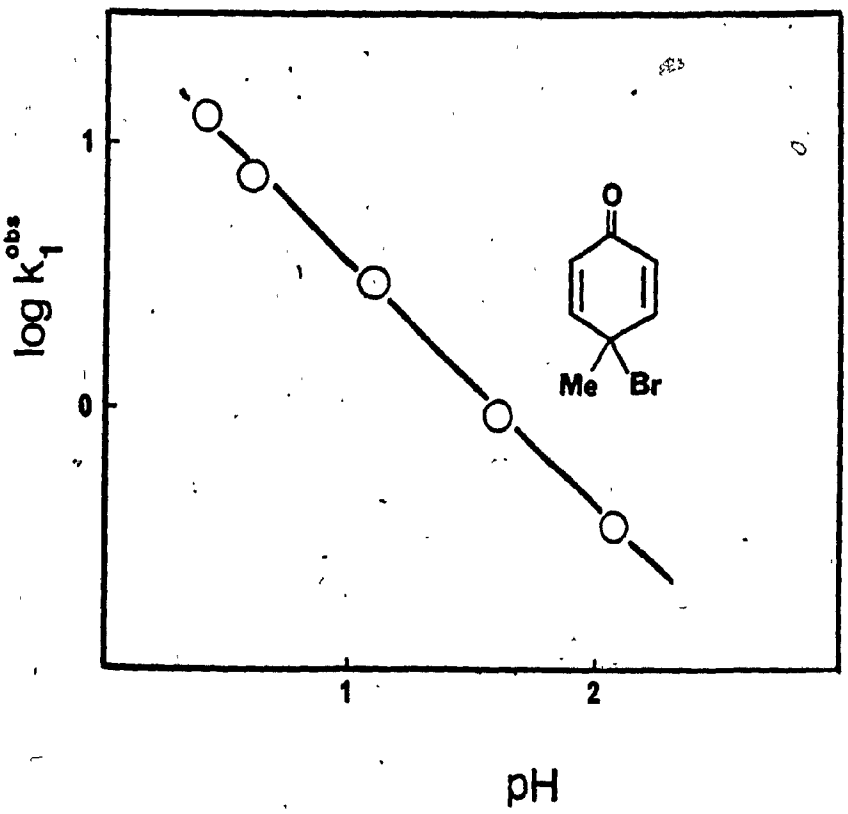
In order to ascertain whether or not there exists an acidity dependence in the debromination rate-catalysed pathway, pH studies were conducted between pH 0-2 in the presence of 5mM cyclodextrin. The ipso intermediate generated under phenol trap conditions, shows no abnormal rate behaviour with increasing pH, as shown in Figure 9.

An attempt at observing buffer catalysis for the intermediate breakdown in the presence of cyclodextrin proved fruitless. Here, the catalysis by α-cyclodextrin on the debromination rate was several times greater in magnitude than that reported for buffer catalysis of 1b[30] resulting in no noticable rate enhancement due to the buffered medium.

Since it has been determined that the debromination of 1b shows rate catalysis in the presence of α-cyclodextrin, experiments were performed on a series of ipso-dienones generated from various p-alkylphenols (see Figure 10). By doing so, it was hoped that a more definite picture of the catalysed pathway would be obtained since steric effects may be important.

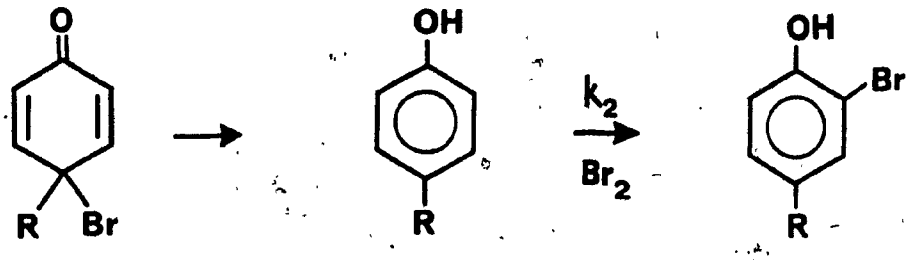
In the absence of cyclodextrin the compounds 1o-1r all show a pH-rate dependence comparable to 1b as shown in Figure 11. Likewise, 1e shows analogous pH-dependence.[30] Phenol trap experiments were performed on these compounds in the presence of varying cyclodextrin concentrations. As found for 1b, significant rate catalysis was observed in all cases. The first-order rate constants exhibit as much

Figure 9: pH-Rate Profile for the Debromination Reaction of the Ipso-dienone of 1b at Constant Cyclodextrin Concentration



Intermediate generated under trap conditions, 0.1M KBr, 5mM CD. pH values corrected according to ref. (51), (Data from Table XVIII, Appendix)

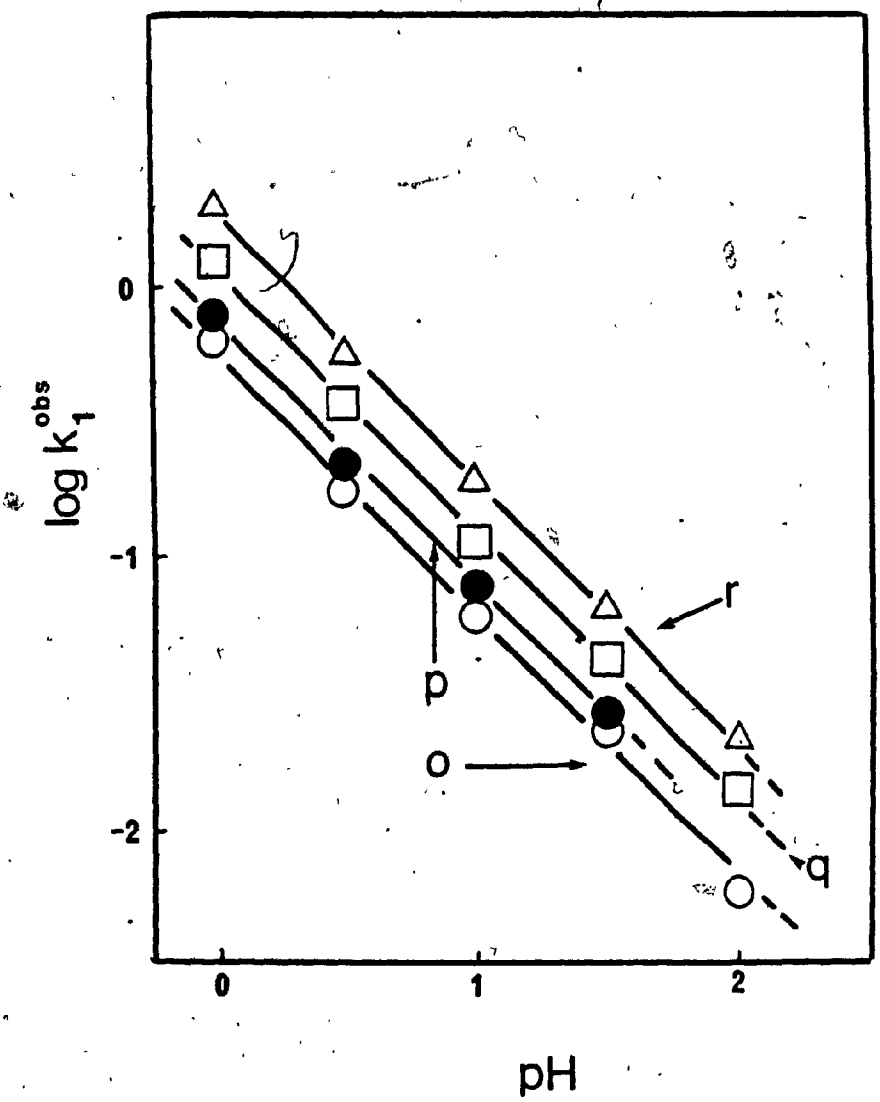
Figure 10: Compounds Which Undergo an Ipso-dienone Debromination Mechanism



3 1

1b	:	R= Me
o		R= Et
p		R= i-Pr
q		R= n-Pr
r		R= 3,4-diMe
e		R= t-Bu

Figure 11: pH-Debromination Rate Profiles for Compounds 1o-1r



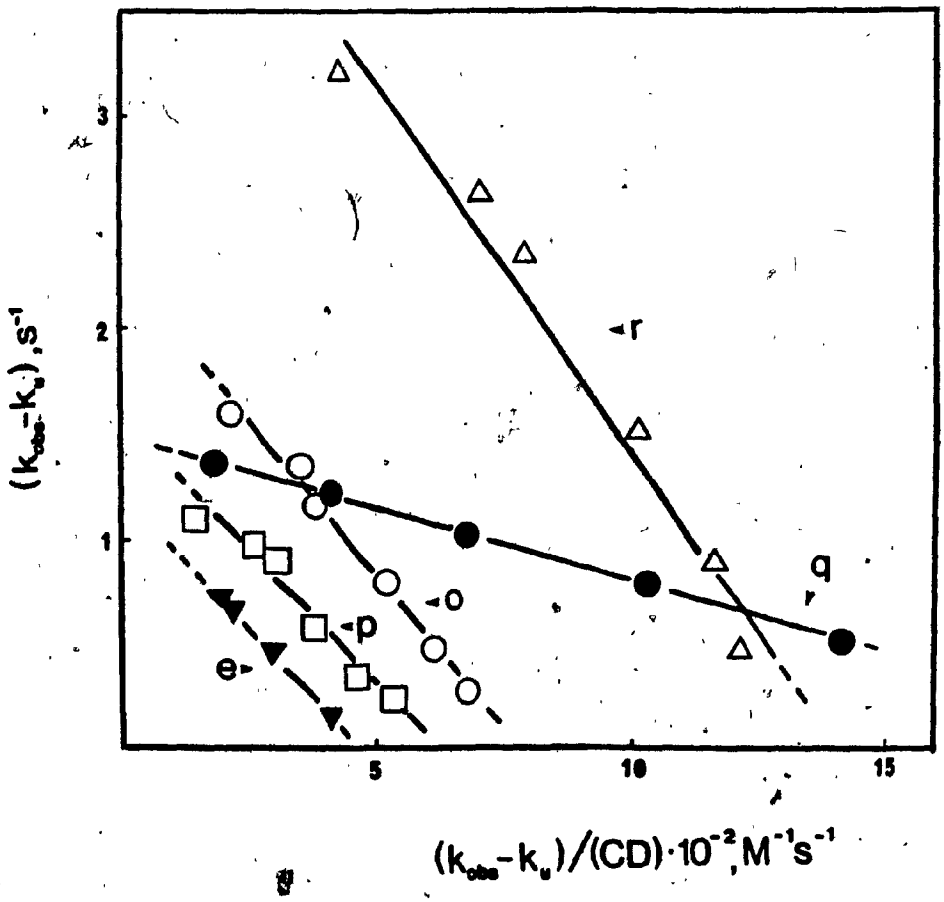
Results from Appendix, Table XIX. All experiments at 0.1M KBr, (Sub)= 0.5mM, (Br_2)= 0.1mM

as twenty-eight fold enhancement upon addition of 5mM α-cyclodextrin.

One can presume with reasonable confidence at this point that the ipso-dienones generated from phenols 1o-1r, 1e are influenced by the same catalytic pathway as 1b. This being the case, the experimental first-order rate constants for the debromination of phenols 1o-1r and 1e were treated according to equation 20 (Eadie-Hofstée analysis). Figure 12 depicts the cummulative results for 1o-1r and 1e. It is evident from the resultant slopes that the values for K_I (slopes) vary between ipso-dienones indicating the size of the 4-alkyl substituent does influence the extent to which binding occurs.

Table VIII summarizes the important parameters involved in the debromination reaction of the dienones 1b, 1o-1r and 1e as obtained from equation 20. Although not discussed in great length, the importance of the intercept is in that it involves the term for the catalysed rate constant k_c. Depending on which scheme is believed to govern the catalysed pathway, k_c will vary substantially. Treatment and analysis of this term will be presented in the Discussion section.

Figure 12: Results for the α-Cyclodextrin Catalysed Debromination of Phenols 1o-1r and 1e as Treated by Equation 20 (25°C)



Data from Appendix, Table XX

Table VIII: Summarized Results for α-CD Catalysed Debromination of 1b, 1o-1r and 1e According to Eqn. 20

Substrate	K_I, mM	k_u(exp), s^{-1}	int., s^{-1}	corr.
1b	4.82	0.0520	4.01	0.9821
1o	2.87	0.0591	2.26	0.9923
1p	2.43	0.0709	1.53	0.9731
1q	0.752	0.141	1.51	0.9966
1r	3.54	0.175	4.98	0.9836
1e	2.53	0.0433	1.20	0.9997

Conditions: 0.1M KBr, 0.05N HCl, 25°C

Discussion

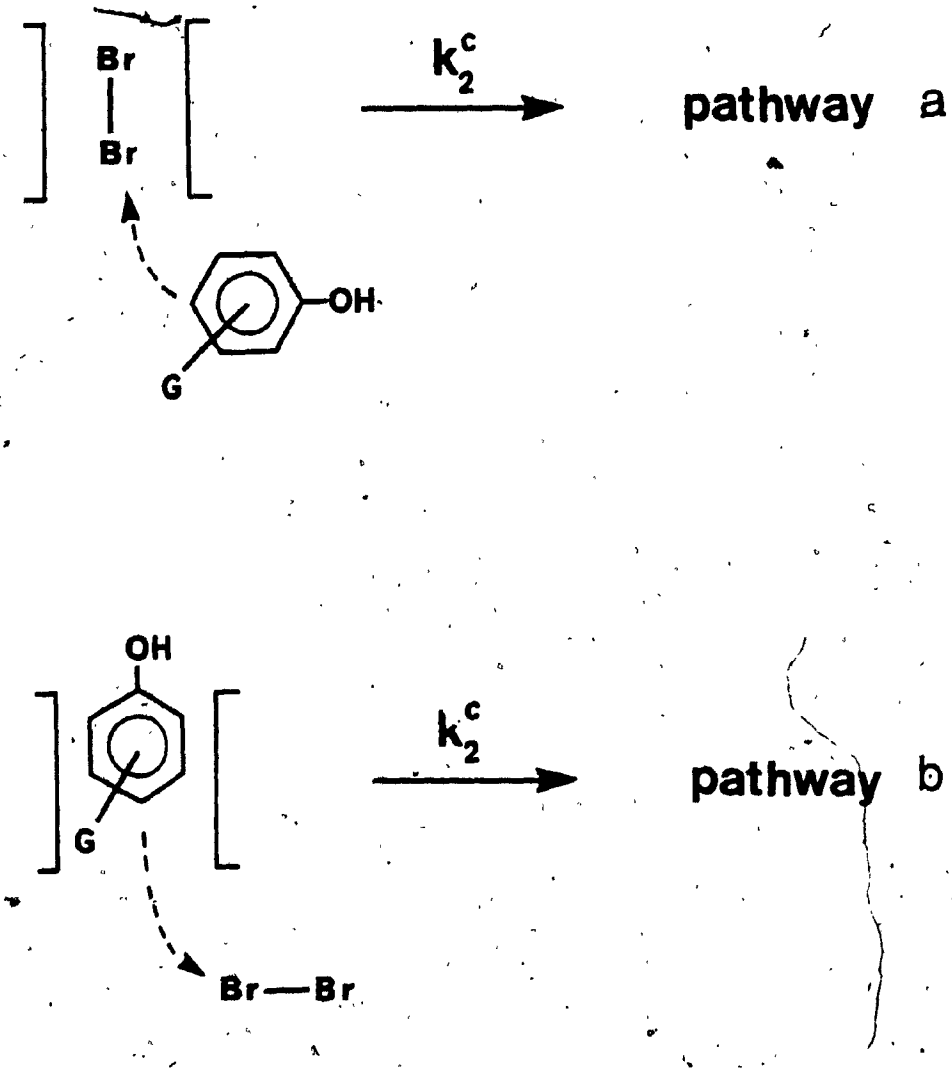
As is evident from the results presented, α-cyclodextrin exerts a remarkable effect on the rate of bromination of phenols. All of the substrates studied react via a catalytic bromination pathway in the presence of α-cyclodextrin which makes up for the rate retardations due to the complexation of reactants.

In the bromination reactions proceeding via the substrate phenol or its ionized form, there exist three possible pathways for the CD-catalysed reaction (Scheme 11):

a) free phenol reacting with complexed bromine
b) free bromine reacting with complexed phenol
c) ternary complex involving α-cyclodextrin, substrate and bromine

As presented earlier, these pathways are kinetically indistinguishable yet possibilities a and b may be differentiated by consideration of substituent effects.

As seen in equations 11 and 12, the term involving the catalytic rate constant k_2^C differs in the significance of the slope obtained for the plot of k_2^{corr}/f_B vs. cyclodextrin concentration. For pathway a, k_2^C = slope x K_B whereas for pathway b, k_2^C = slope x K_S. Thus, the respective values given for k_2^C depend on the magnitudes of K_B (bromine) and K_S (substrate). The dissociation constant K_d is larger than that of K_B by as much as 40



Scheme 11

fold, depending on the phenol. One may argue that based on steric requirements, the catalysed pathway involving complexed bromine reacting with free substrate is the more probable. The size of molecular bromine is much smaller than that of the larger, substituted phenol therefore the requirements of inclusion and subsequent reaction favour complexed bromine.

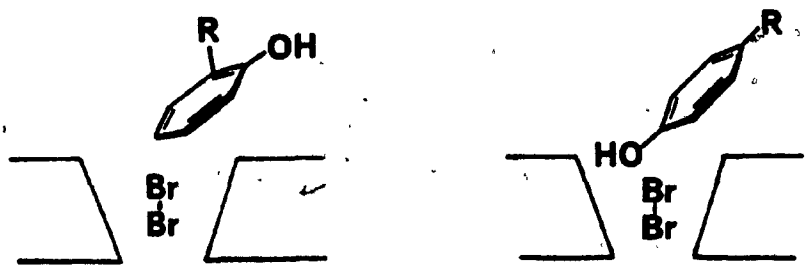
Table IX summarizes the rate constants k_2^C and k_2 obtained using equation 12. The values of k_2^C vary over a range of 50,000 whereas those of k_2 have a range of 10,000. Moreover, as will be made more apparent later, there is a strong correlation between the two sets of values. Table IX also gives the ratios k_2^C/k_2 which measure the efficiency of catalysis as a function of substituent. This ratio only varies between 3 and 28. Thus, for substrates having a wide range of reactivity ($\sim 10^4$) the extent of catalysis is much the same. Furthermore, the values of the ratio seem to fall into two groups. For substrates (1a, 1c, 1d, 1i) having a vacant para position (where reaction takes place) the ratio is higher (14-28) than for the substrates constrained to react at an ortho position (ratios 3-8).

Assuming the catalysed reaction involves pathway a, a steric or geometric argument may be used to explain the reduced efficiency of the catalysis for the 4-substituted phenols towards complexed bromine. As depicted in Scheme 12, para attack at a 2-substituted phenol can take place

Table IX: Rate Parameters for the CD-mediated Bromination of Phenols, obtained from eq. 12[a]

Phenol	No.	$k_2 \times 10^{-5}$	$k_2^C \times 10^{-6}$	k_2^C/k_2
H	1a	4.11	7.39	18.0
4-Me	1b	6.24	4.98	7.98
2-Me	1c	16.2	45.6	28.1
2,6-diMe	1d	12.0	22.5	18.7
4-t-Bu	1e	5.86	1.77	3.02
2-Br	1i	0.101	0.141	14.0
4-Br	1j	0.0389	0.0179	4.60
4-COOEt	1k	0.0155	0.00704	4.54
4-CN	1l	0.00155	0.000926	5.97

a. Units of k_2 and k_2^C are $M^{-1}s^{-1}$ (25°C)



Scheme 12

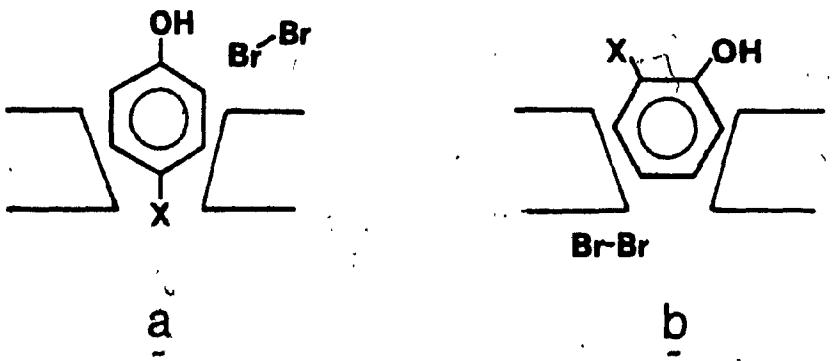
with the hydrophilic OH group in the aqueous medium. On the other hand, for ortho attack on a 4-substituted phenol the OH group is towards the cyclodextrin "lip" and the 4-substituent is directed towards the solvent. Alternatively, it may simply be that it is slightly easier for an unencumbered para position to approach the bromine in the cyclodextrin cavity than for an ortho position which is necessarily flanked by hydroxyl.

In any event, the difference in behaviors of the 2- and 4-substituted phenols is relatively small. A rate ratio of 20 (typical for para attack) corresponds to a $\Delta\Delta G^{\dagger}$ of 1.77kcal/mole whereas a ratio of 5 (for ortho attack) is equivalent to 0.95kcal/mole. Thus, in energy terms, the distinction between the two cases is not large.

Indeed, much larger differences were anticipated. If the data for the catalysed reaction are analysed in terms of pathway b (free bromine attacking complexed substrate), the rate ratios (k_2^C/k_2) fall in the range 3-430.

However, within this range there are no clear trends or obvious groupings according to the nature or position of the substrate. For phenol, itself, the ratio is 430, for 2-substituted phenols the values are 23-346, and for 4-substituted derivatives the range is 3-290. Within each grouping there are no apparent correlations between the rate ratios and the electronic or steric nature of the substituent. For reaction between free bromine and complexed substrate one would have expected a clearer difference between 2- and 4-substituted phenols.

For p-substituted phenols the ortho positions are above the lip of the cyclodextrin cavity and should be reasonably accessible for reaction (Scheme 13a). In contrast, the reactive para position of a 2-substituted phenol is embedded in the cyclodextrin cavity and should be difficult to approach by bromine from the outside (Scheme 13b).



Scheme 13a,b

Accordingly, 4-substituted phenols should show larger rate ratios than 2-substituted phenols for reaction via pathway b. They do not.

In contrast, trends in the data analysed for pathway a are quite reasonable. As discussed above there is a small, but significant difference between 2- and 4-substituted phenols. However, the principle observation is that substituent effects for uncatalysed and catalysed pathways are essentially the same. Figure 13 show a plot of log k_2^C (for pathway a) vs. log k_2. The slope of this line ($r = 0.9872$) is 1.1. Thus, the sensitivity of k_2^C to substituent change is just slighty greater than that of k_2.

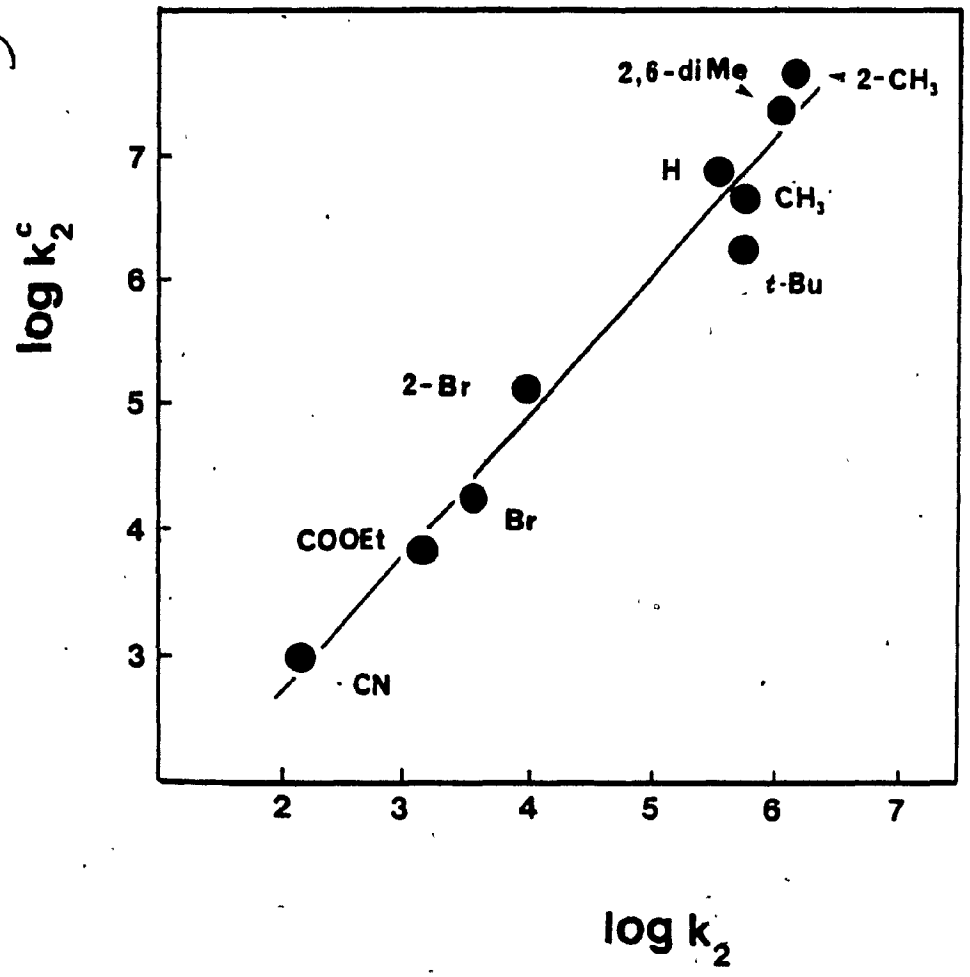
Figure 13 can be regarded as relating k_2^C to k_2 as a function of the substituent on the phenol. As such it is the superimposition of two Hammett plots with slightly different slopes. Conventional Hammett plots relate a given rate constant k to the substituent variable.[43]

$$\log k = \log k_0 + \rho\sigma$$

The term ρ, the slope of the plot is the reaction variable.

Hammett's original proposal involved the use of pKa values of benzoic acids as the basis of the scale of values. The value of σ is, by definition, one for the ionization of substituted benzoic acids. For a given reaction ρ measures the sensitivity of the reaction to the change in

Figure 13: Plot of log k_2^c vs. k_2 for Parent Phenols 1a-1e, 1i-1l Treated According to eq.12



The slope of the line is m= 1.1

substituents.

The slope of Figure 13 is essentially unity. In terms of the Hammett approach, this means that the ρ values for k_2^C and k_2 are, in essence, the same. Thus, the catalysed and uncatalysed pathways are equally sensitive to the nature of the substituent on the phenol, whether it be electron-withdrawing or electron-releasing. Moreover, the fact that is unchanged for the catalysed reaction supports a reaction pathway proceeding via an unrestricted or free phenol reacting with complexed bromine, since the pattern of phenol reactivity isn't substantially changed due to complexed bromine.

Also, since the reaction variable is essentially unchanged in the catalysed reaction, it can be concluded that the α-cyclodextrin does not show any covalent catalysis. By not taking part in the catalysed reaction, the molecule in essence is providing an environment favourable towards reaction ie. non-covalent catalysis.

If the data had been treated according to eq. 11, namely free bromine reacting with complexed substrate phenol (pathway b, Scheme 11), the calculated values obtained for k_2^C would be increased by one or two orders of magnitude. Subsequent plotting of log k_2^C vs log k_2 showed extreme scatter and poor linearity. As discussed earlier, there are no obvious trends in the way in which k_2^C varies with k_2 as a function of the nature or the position of the substituent for this pathway.

Taken as a whole, the data for the CD-catalysed bromination of phenols make much more sense when considered in terms of pathway a. The cyclodextrin provides an environment slightly different from that of the bulk medium and in which bromine is somewhat more reactive.

Bromination of Phenoxide Ions

The present results for reactions proceeding via the anionic form of the phenols provide additional evidence which supports a non-covalent catalysed reaction pathway involving complexed bromine reacting with free substrate. The uncatalysed rate constants for these reactions are all of greater magnitude than if reaction proceeded by the unionized form.

Table X shows the rate parameters and catalytic rate ratio for phenols 1f-1k as treated according to case a where:

$$\frac{k_2^{corr}}{f_B} = \frac{K_a}{[H^+]}\left(k_2 + \frac{k_2^c[CD]}{K_B}\right) \qquad 21$$

Of striking interest are the magnitudes of the catalysed rate constants. These values all reside very near the diffusion-controlled limit for reaction, with the greatest catalysed rate constant belonging to m-nitrophenol (1h).

Results reported earlier in this thesis regarding a possible bromide ion dependence of the cyclodextrin-mediated bromination of 1h showed no significant contribution by the tribromide ion in the reaction. This result is

Table X: Rate Parameters for the Bromination of Anions of Phenols 1f-1k as Treated by eq. 21[a]

Phenol	No.	$k_2 \times 10^{-9}$	$k_2^c \times 10^{-9}$	k_2^c/k_2
4-NO_2	1f[b]	1.15	7.45	6.48
2-NO_2	1g	1.60	12.0	7.50
3-NO_2	1h	4.17	59.0	14.1
2-Br	1i	6.16	16.5	2.68
4-Br	1j	10.7	41.6	3.89
4-CN	1k	3.13	12.2	3.90

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

b. Average results.

in disagreement with reported results[22] where it was found that 2% of reaction is attributed to the participation of the tribromide ion in the normal bromination. In the catalysed reaction however, the enhanced reactivity of molecular bromine may simply swamp the effect of the tribromide ion as a bromination species.

The magnitude of k_2^C provides additional support for pathway a as the catalytic mechanism. The resultant slope, as treated by equation 21, would be equal to k_2^C/K_B after consideration of the ionization ratio $Ka/(H^+)$. The values for k_2^C as shown in Table X are of the order of 10^9-10^{10} $M^{-1}s^{-1}$. These rate constants are at the diffusion-controlled limit for reaction as discussed in reference (25). Alternatively, the data treatment required for pathway b produces catalytic rate constants between 10^{11}-10^{12} $M^{-1}s^{-1}$! Clearly, the magnitude of these rate constants are undisputably above the diffusion-controlled rate as defined by numerous sources.[25,44]

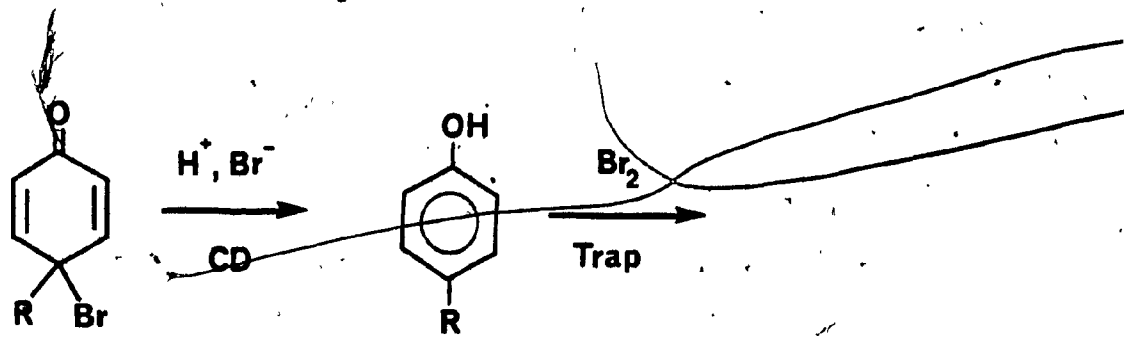
The magnitude of the catalytic ratio for the reaction proceeding via the ionized form of phenols 1f-1k follow the general trend of meta > ortho > para. The three nitro isomers of phenol (1f-1h) exhibit this trend in the values of both the uncatalysed and catalysed rate constants obtained. This observation tends to substantiate the arguments in favour of pathway a. Since the substituent effects for the uncatalysed and catalysed pathways are much the same, it seems reasonable that the substrate is outside

the cyclodextrin cavity and in a largely aqueous environment when the reaction takes place.

The slightly lower ratios of k_2^C/k_2 which are shown for para substituents compliment those found in phenol bromination. They presumably have similar steric origins.

Ipso-dienone Debromination

The cyclodextrin-mediated debromination of the ipso-dienones of phenols 1b, 1e, and 1o-1r exhibits substantial catalysis, as presented earlier. Also, the reaction shows proton and bromide ion catalysis at constant cyclodextrin concentration. These results are consistent with a CD-catalysed debromination analogous to the reaction observed in the absence of cyclodextrin.



As a consequence of the Principle of Microscopic Reversibility one expects to see catalysis by cyclodextrin for the debromination reaction 3-1 since the bromination of phenols exhibits catalysis (see above). In keeping with the Principle and since the forward reaction appears to involve

complexed bromine reacting with free phenol 1, the debromination of 3-1b must involve uncomplexed intermediate reacting with complexed bromide ion (see eqn. 20). At first glance this appears unlikely since the respective complex dissociation constants K_I and K_1 are considerably different in magnitude ($\simeq$3mM and 0.286M[9]). This means that binding by the ipso-dienones is much stronger than that of the bromide ion and so intuitively one anticipates a reaction of complexed dienone. Under the experimental conditions used, however, the total concentration of bromide ion is large enough that a sizable proportion of the cyclodextrin is present as complexed ion. Once encapsulated, the ion may react by the mechanism shown above.

Assuming then that the catalysed reaction 3-1 involves complexed bromide ion, data interpretation and treatment by the Eadie-Hofstee method (eqn. 20) takes the form of:

$$k^{obs} - k_u = \frac{-K_I(k^{obs} - k_u)}{[CD]} + \frac{k_c K_I}{K_1} - k_u \qquad 22$$

Table XI summarizes the rate constants k_u and k_c and the catalytic rate ratio for the ipso-dienones 1b, 1e and 1o-1r undergoing debromination by this model.

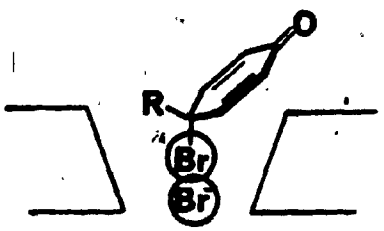
The extent of catalysis, as shown by the ratio k_c/k_u, is large, ranging from 2300 to 4600. Most

Table XI: Rate Parameters for the Debromination of the Phenols 1b, 1e, and 1o-1r as Treated by Equation 22.[1]

Phenol	R	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u
1b	Me	0.0520	238	4580
1o	Et	0.0591	225	3810
1p	i-Pr	0.0709	180	2540
1q	n-Pr	0.141	574	4070
1r	3,4-diMe	0.175	402	2300
1e	t-Bu	0.0433	136	3130

Data obtained from reactions conducted in 0.1M KBr, 0.05N HCl with an excess of phenol as a bromine trap. Values of k_u were experimentally determined, they are not intercept values.

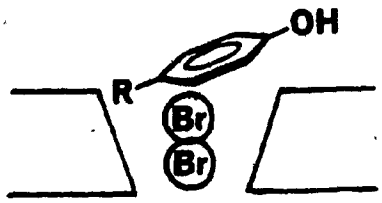
remarkable is that the ratio is very similar (only a range of two fold) for substituents of varying length (1-4 carbons) and size (Me- t-Bu). Moreover, with the disubstituted compound 1r (R= 3,4-diMe) the amount of catalysis is similar to that for the monosubstituted compounds. These observations are consistent with the formation of a transition state in which the alkyl group R is outside of and away from the cyclodextrin cavity so that to a first approximation its size and shape is of little consequence (see below).



Scheme 14

This arrangement can most easily be attained from reaction of free dienone with complexed bromide ion.

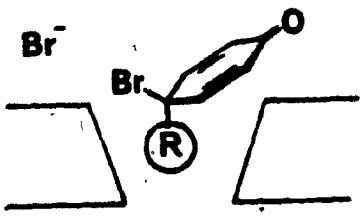
The above model also has the virtue that it is compatible with the conclusions of the bromination studies, discussed earlier. There, it was argued that reaction arises from free phenol and complexed bromine (see Scheme 15). Again it is emphasized that since bromination and debromination are the microscopic reverse of one another they



Scheme 15

must have identical transition states.

An alternative to the proposed model for catalysis involves the reaction of free bromide ion with complexed ipso-dienone. The mostly likely arrangement for this would involve the alkyl group R inside the CD cavity and the ipso-bromine outside, accessible to attack by Br^- (see Scheme 16 below).

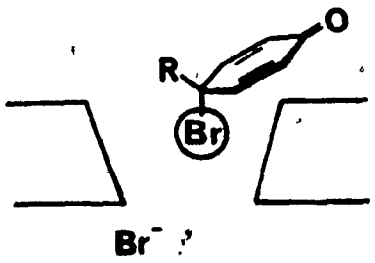


Scheme 16

For this model the appropriate rate ratio (k_c/k_u) vary only from 12-78. This seems quite unlikely given again the variability in R both in respect to chain length and steric bulk. In particular, for R= Et, i-Pr, t-Bu and for the 3,4-diMethyl compound the ratio is virtually constant

(39, 23, 28, and 29, respectively). For these different sized groups the dienones should sit progressively higher in the CD cavity and so attack at the ipso-bromine should be easier.

It is also noteworthy that the values of K_I for the ipso-dienone/CD complexes do not vary greatly. For R= Me, i-Pr, t-Bu and the 3,4-diMethyl derivative the respective values (in mM) are: 4.8, 2.9, 2.4, 2.3, and 3.5. Again, this lack of variability makes little sense if the binding of the dienones is largely due to the presence of the alkyl group R in the CD cavity. The binding constants of alcohols, alkylphenols and alkylphenyl acetates, for example, show a much wider variation with the nature of the alkyl group.[45] However, the lack of variability for the dienone K_I values is reasonable if it is the ipso-bromine which enters the cyclodextrin cavity (see Scheme below).

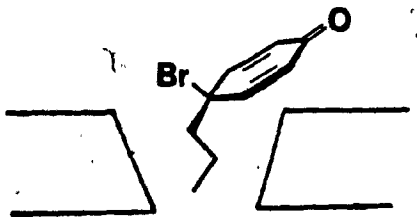


Scheme 17

This orientation is not unreasonable since bromine bound to carbon has a lipophilicity similar to that of the alkyl groups present in the ipso-dienone.[45]

A possible exception to the binding portrayed above

is the case of R= n-Pr. For this the binding is appreciably stronger (K_I= 0.75M). This may represent alkyl group binding where the extended propyl chain can better occupy the CD cavity (Scheme 18).



Scheme 18

In the above discussion two conceivable modes of binding have been ignored. Firstly, the mode in which the dienone binds with its carbonyl group in the cavity of the cyclodextrin: This mode is considered to be most unlikely since the carbonyl is the most hydrophilic part of the ipso-dienone and hydrophobic interactions are of primary importance.[45] Secondly, the simultaneous binding of the bromine and the alkyl group of the ipso-dienone in the CD cavity has been rejected. Space-filling models, which have been extremely useful in analyzing results and designing novel systems[1,17] clearly show that such simultaneous binding is sterically not feasible.

In summary, the results from the study of catalysis of debromination of ipso-dieonones appear reasonable for a reaction between encapsulated bromide ion and free dienone.

This conclusion is also consistent with that arrived from bromination studies, viz. that free phenol reacts with the cyclodextrin-bromine complex.

Throughout this study, the possibility of a discrete ternary complex promoting catalysis has not been extensively addressed. This pathway for catalysis is kinetically indistinguishable from those discussed in data analysis for the phenols and the ipso-dienone intermediates. Evidence for the intermediacy of such a complex has been cited for the α-cyclodextrin-mediated Riemer-Tiemann reaction.[46]

The formation of such complexes where both reactants would be complexed to varying extents could promote reaction. The presence of cyclodextrin would essentially facilitate the approach of the reactants to each other. Such a pathway would satisfy the proposed steric and substituent arguments presented for the bromination and debromination processes, assuming that the ternary complex had the sort of geometries depicted earlier.

Unfortunately, the presence or absence of a ternary complex cannot be adduced from the present data. The formation of such a complex would only distort Michaelis-Menten kinetics if its dissociation constant was in the concentration range studied. Such is clearly not the case.

Whether the reaction involving cyclodextrin proceeds by a ternary complex or not, the rate data presented in all cases supports the process involving non-covalent catalysis by α-cyclodextrin. The cyclodextrin may lower

the barrier to reaction by bringing the reactants together with greater ease and in a relative geometry that is appropriate for reaction if a ternary complex is involved.

Conclusion

The kinetic evidence and arguments presented in this thesis support a α-cyclodextrin-mediated bromination involving a non-covalent pathway. Catalytic rate constants were greater than the uncatalysed rate constants by as much as one order of magnitude for the phenols reacting both with the parent and anionic forms. Steric and reactivity arguments support a non-covalent mechanism involving the reaction of free phenol with the CD-bromine complex.

In the debromination of the ipso-dienones formed from p-alkylphenols, the kinetic results show remarkable acceleration in the presence of α-cyclodextrin. Here, the catalytic pathway which is operating is thought to involve complexed bromide ion reacting with free ipso-dienone. This mechanism is supported by arguments regarding steric, geometric and kinetic theory pertaining to reaction reversibility.

The studies of both bromination and debromination in the presence of α-cyclodextrin lead to a consistent picture for the reaction transition state, as they should. It is argued that in the transition state the two bromine atoms involved are basically in the CD cavity whereas the organic moiety (and its substituents) are essentially outside of the cavity and in a largely aqueous environment. Accordingly, substituent effects for the catalysed and uncatalysed reactions are closely similar.

The involvement of a ternary complex (substrate,

reagent, CD) is mooted but the present results shed little light on this possibility. The formation of such a complex could facilitate reaction by bringing the reactants together and in a favourable arrangement.

Experimental

All substrate phenols and α-cyclodextrin used in this study were obtained from commercial sources. In cases where impurities were present, the samples were purified by recrystallizations or distillation.

The substrate phenols used in kinetic and spectral studies originated from 0.1-0.5M stock solutions prepared in analytical grade methanol for solubility reasons. Aqueous α-cyclodextrin stock solutions of 0.1M at fixed pH and ionic strength were used within twenty-four hours of preparation.

Bromine solutions were prepared by dilution of a small volume of a stock solution (0.05-0.1M in 0.1M KBr) with the desired medium. The parent solution was made by weighing a small amount of liquid bromine into 10mL of 0.1M KBr and diluting to the required concentration.

Although most of the kinetic studies were carried out under dilute acid conditions, pH dependence and experiments on certain substituted phenol bromination experiments required a range of acidities. For these buffer solutions were prepared according to Perrin.[47] All solutions contained 0.1M KBr and, except at higher acidities (pH < 2), the ionic strength was 0.11M. In bromide ion dependence studies, the ionic strength was adjusted to 0.1M by the addition of NaCl. The mixed concentrations of substrate and bromine for stopped-flow experiments ranged from 0.1-0.5mM and 0.01-0.05mM, respectively.

Ipso-dienone - Phenol Trap Experiments

These experiments required considerably more manipulation than conventional stopped-flow studies. Solutions of 0.4mM substrate and bromine were prepared at a fixed pH ≈ 4.5 in the absence of added bromide ion. 5mL of each were pipetted into a common container in order to generate a solution of the ipso-dienone intermediate (≈0.02M). This solution was then mixed in the stopped-flow chamber with a phenol solution (0.4mM before mixing) containing twice the required KBr concentration and acid or buffer of the desired pH. Immediately after mixing the concentrations of the ipso-dienones and phenol (bromine trap) were 0.1mM and 0.2mM respectively, at the bromide ion concentrations cited. The presence of the large excess of phenol assures the rapid consumption of liberated bromine, as previously discussed.

Spectral Studies

Complexation dissociation constants were determined on either an Aminco DW-2 UV-Visible or Cary 2290 spectrophotometer under constant temperature conditions (25°C). Monitoring wavelengths were between 310-380nm. Substrate solutions of 0.1mM at fixed pH and ionic strength contained various α-cyclodextrin concentrations between 0-0.01M. Data analysis used a Hildebrand-Benesi approach as previously discussed[20,21].

Kinetic Studies

The kinetics of bromination were examined using an Aminco DW-2 UV-visible spectrophotometer operating in the dual beam mode with stopped-flow accessory.[48] The cell was thermostatted at 25°C+.1°C. Due to the gradual reaction of α-cyclodextrin with bromine, the stopped-flow experiments involved the mixing of equal volumes of CD/substrate phenol in buffer (syringe #1) with a bromine/buffer solution (syringe #2). The second-order bromination process was monitored by the decrease in absorption at 275nm due to the tribromide ion. Under the conditions used (a ten-fold excess of substrate over bromine), the reactions showed ideal pseudo first-order kinetics. For the ipso-dienones, the first-order decay was monitored between λ_{max} 240-250nm.

Data aquisition used the apparatus and methods previously described.[49] Least-squares analysis of ln $(A-A_\infty)$ versus time showed good linearity (r=.9995). The reported first-order rate constants are averages of four individual runs. They were converted to apparent second-order rate constants by division by $((S)_0-(Br_2)_0)$ for reasons given elsewhere.[50]

Most of the kinetic data analysis used the normal or observed A_∞ in first-order rate constant determinations. However, in analysis of the cyclohexadienone breakdown, the Swinbourne value for A_∞ was employed. This was due to the presence of slight spectral tailing even under trap

conditions.

The computer programs used in this study were as follows: TRIST, ACTIVE, NEWEQN, LINEW and INTFIT. These were written in BASIC by Dr. O.S. Tee and used in successful data analysis.

The programs NEWEQN, LINEW and INTFIT were developed specifically for the reactions and equations introduced in this and previous work.[20,21] NEWEQN was used to obtain results based on equation (12), linearly correlating k_2^{corr}/f_B with cyclodextrin concentration.

LINEW was used for spectral and kinetic determinations based on the Lineweaver-Burke and Eadie-Hofstée data treatments specific to this study (equations 20 and 22). The INTFIT program, based on non-linear least-squares fitting techniques, was used to substantiate the kinetic results obtained.

The determination of the pH values at higher acidity (pH < 2) was based on the Davies equation[51] (ACTIVE program) which considers the H^+ activity in calculating pH values.

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Appendix

Table XXI: Apparent Second-order Bromination Rate Constants for Phenols 1b-1e as a Function of Cyclodextrin Concentration

Phenol	(CD), mM	$k_2^{app} \times 10^{-5} M^{-1} s^{-1}$
1b: 0.1M KBr, pH= 2.07	0	2.37
	0.10	2.39
	0.25	2.37
	0.50	2.39
	1.00	2.38
	2.00	2.28
	5.00	2.09
1b: 0.05M KBr, pH= 2.08	0	3.12
	0.10	3.21
	0.25	3.42
	0.50	3.39
	1.00	3.51
	2.00	3.47
	5.00	3.33

Table XII continued...

1c: 1.0M KBr, 0.01N HCl	0	0.86
	0.50	1.35
	1.00	1.42
	2.00	1.49
	4.00	1.50
	5.00	1.53
1d: 0.1M KBr, 0.01N HCl	0	4.31
	0.25	5.68
	0.50	6.41
	1.00	7.46
	2.00	8.47
	5.00	8.26
1e: 0.1M KBr, 0.1N HCl	0	2.11
	0.50	1.26
	1.00	1.04
	2.00	0.859

Phenols 1b, 1d, 1e: (Sub)= 0.10mM; (Br_2)= 0.01mM

Phenol 1c: (Sub)= 0.5mM; (Br_2)= 0.05mM

Table XIII: k_2^{app} vs. Cyclodextrin Concentration for the Bromination of Phenols 1i-1k (Parent Forms)

Phenol	(CD), mM	$k_2^{app} \times 10^{-5} M^{-1} s^{-1}$
1i: 0.1N HCl	0	3.62
	0.25	4.67
	0.50	5.11
	1.00	5.40
	2.00	5.60
	4.00	5.60
	5.00	5.53
	10.0	5.31
1j: 0.1N HCl	0	1.40
	0.25	1.04
	0.50	0.851
	1.00	0.624
	2.00	0.424
	4.00	0.260
	5.00	0.224
	10.0	0.128

Table XIII continued...

1k: 1.0N HCl	0	0.0558
	0.50	0.0444
	1.00	0.0427
	2.00	0.0369
	4.00	0.0298
	5.00	0.0269
1l: 1.0N HCl	0	0.558
	0.50	0.378
	1.00	0.320
	2.00	0.256
	4.00	0.197
	5.00	0.177
	10.0	0.124

Conditions: (Sub)= 0.50mM; (Br_2)= 0.05mM; 0.1M KBr

Table XIV: Apparent Second-order Bromination Rate Constants for the Bromination of Phenol (1f) as a Function of α-Cyclodextrin Concentration (25°C)

	(CD), mM	$k_2^{app} \times 10^{-3} M^{-1} s^{-1}$
0.1M KBr, pH= 2.07	0	4.44
	0.10	4.33
	0.25	4.09
	0.50	3.76
	1.00	3.36
	2.50	2.73
	5.00	2.04
	7.50	1.64
	10.0	1.39
0.05M KBr, pH= 2.09	0	6.67
	0.10	6.58
	0.25	6.44
	0.50	6.29
	1.00	5.91
	2.50	4.89
	5.00	3.69
	7.50	3.02
	10.0	2.47

Table XIV continued...

0.1M KBr, pH= 2.93	0	35.8
	0.25	29.6
	0.50	26.9
	1.00	23.1
	2.50	18.4
	5.00	14.4
	7.50	11.9
	10.0	10.2
0.05M KBr, pH= 2.92	0	46.9
	0.25	42.4
	0.50	38.9
	1.00	35.3
	2.50	29.1

Concentrations of phenol and bromine are 0.5mM and 0.05mM respectively (all experiments).

Table XV: pH-Rate Profiles for the Bromination of Phenols 1f-1k, 1l

Phenol	pH	$k_2^{obs} \times 10^2$ $M^{-1}s^{-1}$
1f	0.30	2.75
	0.50	4.26
	0.70	6.16
	0.88	9.12
	1.10	14.8
	2.08	123.0
	2.93	1000.0
1g	1.10	1.55
	1.59	45.7
	2.02	132.0
	2.45	363.0
	2.82	933.0
1h	2.49	3.09
	3.25	17.8
	4.09	123.0
	5.18	1550.0

Table XV continued...

11	0.10	1.55
	1.10	7.08
	2.08	46.8
	2.96	347.0
	4.07	3980.0
1d	0.10	9550
	1.10	19000
	1.59	20400
	2.08	20000
	2.38	20000
	2.87	20400
	3.97	20400

Conditions: Phenol Trap

pH values < 2.08 were calculated according to the Davies equation (based on H^+ activity)[50]

Table XVI: Apparent Second-order Rate Constants as a Function of α-Cyclodextrin Concentration (25°C)

Substrate	(CD), mM	$k_2^{app} \times 10^{-3} M^{-1} s^{-1}$
1g	0	4.58
	0.50	4.38
	1.0	4.29
	2.5	4.11
	4.0	3.89
	5.0	3.78
	10.0	3.51
1h	0	0.671
	0.50	0.878
	1.0	0.898
	2.0	0.847
	4.0	0.740
	5.0	0.702
	10.0	0.533
1i	0	273.0
	0.50	171.0
	1.0	139.0

Table XVI continued...

1i	2.0	114.0
	5.0	96.2
	10.0	92.8
1j	0	62.7
	0.25	46.2
	0.50	36.9
	1.0	25.3
	2.0	17.1
	4.0	10.4
	5.0	8.62
	10.0	4.87
1k	0	1.91
	0.50	1.26
	1.0	1.09
	2.0	0.891
	4.0	0.702
	5.0	0.611
	10.0	0.456

* All concentrations: (Sub)= 0.5mM; (Br_2) = 0.05mM except 1i where concentrations were 0.01mM and 0.01mM respectively. All solutions at 0.1M KBr. pH values were 2.02, 1.89, 4.40, 4.57, and 2.07 for the series g-k.

Table XVII: Observed Rate of Debromination of Phenol 1b as a Function of α-Cyclodextrin Concentration (0.05N HCl)

Conditions	(CD), mM	k_1^{obs}, s^{-1}
0.1M KBr	0	0.0520
	0.50	0.337
	1.0	0.605
	2.0	0.930
	4.0	1.58
	5.0	1.86
	10.0	2.49
0.2M KBr	0	0.0764
	0.50	0.526
	1.0	0.898
	2.0	1.54
	4.0	2.62
	5.0	2.91
	10.0	3.67
0.1M KBr (0.50N HCl)	0	0.427
	0.50	2.52
	1.0	4.42

Table XVII continued...

	2.0	7.44
	4.0	11.0
	5.0	12.9
	10.0	15.7
0.05M KBr, 0.05M NaCl	0	0.0262
	0.50	0.167
	1.0	0.299
	2.0	0.510
	4.0	0.845
	5.0	0.955
	10.0	1.35
0.075M KBr, 0.025M NaCl	0	0.0381
	0.50	0.225
	1.0	0.396
	2.0	0.657
	4.0	1.09
	5.0	1.20
	10.0	1.51

Table XVIII: pH-Rate Data for the Debromination of the Ipso-dienone of 1b at Constant CD Concentration (5mM)

pH	k_1^{obs}, s^{-1}	log k_1^{obs}
0.42	12.9	1.11
0.61	7.21	0.858
1.10	3.06	0.486
1.39	1.75	0.243
1.59	1.14	0.0569
2.08	0.317	-0.499

Conditions: 0.1M KBr, pH calculated according to (51)
Phenol Trap conditions

Table XIX: pH-Debromination Rate Profile for Substrates 1o-1r (0.1M KBr)

Substrate	pH	k_1^{obs}, s^{-1}	log k_1^{obs}
1o	0	0.624	-0.205
	0.5	0.177	-0.752
	1.0	0.0598	-1.22
	1.5	0.0223	-1.65
	2.0	0.00545	-2.26
1p	0	0.755	-0.122
	0.5	0.210	-0.678
	1.0	0.0716	-1.14
	1.5	0.0255	-1.59
1q	0	1.29	0.110
	0.50	0.349	-0.457
	1.0	0.112	-0.951
	1.5	0.0415	-1.38
	2.0	0.0135	-1.87
1r	0	2.00	0.301
	0.50	0.547	-0.262
	1.0	0.183	-0.737
	1.5	0.0630	-1.20
	2.0	0.0228	-1.64

Table XX: Observed Debromination Rate Constants as a Function of α-CD Concentration for Phenols 1o-1r, 1e

Substrate	(CD), mM	k_1^{obs}, s^{-1}
1o	0	0.0591
	0.50	0.314
	1.0	0.516
	2.0	0.840
	4.0	1.21
	5.0	1.39
	10.0	1.63
1p	0	0.0709
	0.50	0.273
	1.0	0.417
	2.0	0.632
	4.0	0.978
	5.0	1.04
	10.0	1.15
1q	0	0.141
	0.50	0.630
	1.0	0.906

Table XX continued...

1g	2.0	1.15
	4.0	1.36
	5.0	1.41
	10.0	1.48
1r	0	0.175
	0.50	0.622
	1.0	1.04
	2.0	1.68
	4.0	2.52
	5.0	2.82
	10.0	3.39
1e	0	0.0433
	0.50	0.196
	1.0	0.336
	2.0	0.489
	4.0	0.692
	5.0	0.753

Conditions: 0.1N HCl, 0.1M KBr, (S)- 0.1mM, (Br_2)= 0.1mM
(except 1e where 0.05N HCl)
Phenol Trap

Eadie-Hofstée Treatment for Ipso-dienone Debromination Rate Data (eqn. 22)

Given eqn. 18:

$$k^{obs} = (k_u + \frac{k_c[CD]}{K_1}) \cdot f_I$$

the fraction f_I is defined by:

$$f_I = \frac{K_I}{K_I + [CD]}$$

$$K_1 k^{obs} \cdot \frac{(K_I + [CD])}{K_1} = K_1 k_u + k_c[CD]$$

$$K_I K_1 k^{obs} + K_1 k^{obs}[CD] = K_1 K_I k_u + K_I k_c[CD]$$

$$K_I K_1 k^{obs} + K_1 k^{obs}[CD] - k_u K_1[CD] = K_1 K_I k_u + K_I k_c[CD] - K_1 k_u[CD]$$

grouping of like terms and rearrangement gives:

$$(k^{obs} - k_u)[CD] = -K_I(k^{obs} - k_u) + \frac{(k_c K_I - k_u K_1)[CD]}{K_1}$$

$$k^{obs} - k_u = \frac{-K_I(k^{obs} - k_u)}{[CD]} + \frac{k_c K_I}{K_1} - k_u$$

It should be noted that the reaction dependence on Br^- is embedded in the terms k_u and k_c (as is eqn. 19).