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The Effect of α-Cyclodextrin on the Bromination of Organic Compounds

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ABSTRACT

The Effect of α-Cyclodextrin on the Bromination of Organic Compounds

Bushra C. Javed

α-Cyclodextrin (α-CD) significantly affects the rates of bromination of many organic substrates; phenols, salicylate ions, heteroaromatic and aromatic carboxylate ions and pyridones, in aqueous KBr solutions.

The apparent dissociation constants of the transition states (K_{TS}) for phenols, salicylates, pyridones and formate ion are in good agreement with those found for many other substituted phenols studied previously.

The CD-substrate dissociation constants have been determined by an inhibition method for most of the compounds and range from 4.74 to 109 mM. For compounds where this method is not successful, fitted values are used.

The rate changes of bromination of above compounds appear to involve complexed bromine reacting with free substrate. This pathway partially or totally makes up for the rate reductions due to complexation of the tribromide ion, bromine and the substrate. The carboxylate ions show peculiar behaviours, different from that of other compounds in the presence of α-CD.

Relatively large rate enhancement observed for formic acid is solely due to the effect of α-CD on increasing the reactivity of bromine by encapsulation.

The behaviour of α-CD is in accordance with non-covalent catalysis of the bromination, in which a slightly different environment is provided for the reaction by the cavity of α-CD.

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I wish also to thank all other individuals of the department of Chemistry, Concordia University; who provided support during the program.

The financial assistance provided by the department of Chemistry is also gratefully acknowledged.

Dedicated to my parents
and to my children.

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CHAPTER 1

INTRODUCTION

The ability of cyclodextrins (CDs) to form inclusion compounds with a variety of organic substrates has raised a general interest in their physical and chemical properties over the past few years. Due to this ability CDs can have significant effects on the rates of various kinds of reactions.

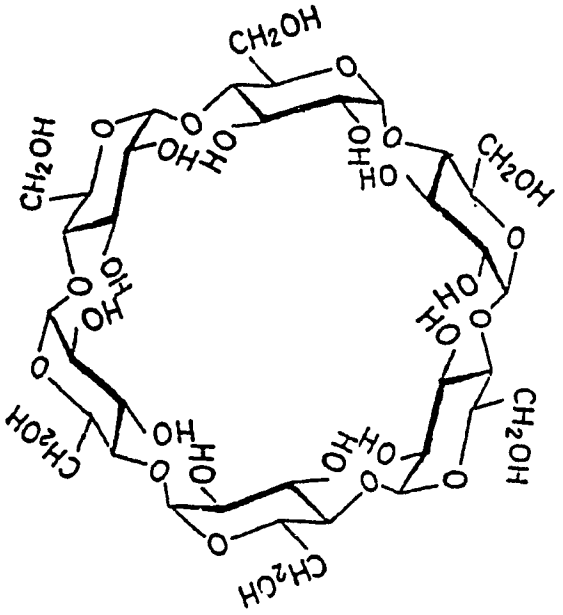
1.1 THE STRUCTURE OF CYCLODEXTRINS

Cyclodextrins are doughnut shaped macro rings built up from α-(1,4) linkages of a number of D(+)- glucopyranose units[1]. They are designated by a Greek letter to denote the number of glucose units. α for 6, ß for 7, for 8 and so on. The structure of α-cyclodextrin (also called cyclohexaamylose or α-CD) having 1-4 glycosidic linkages, is shown in Figure 1.

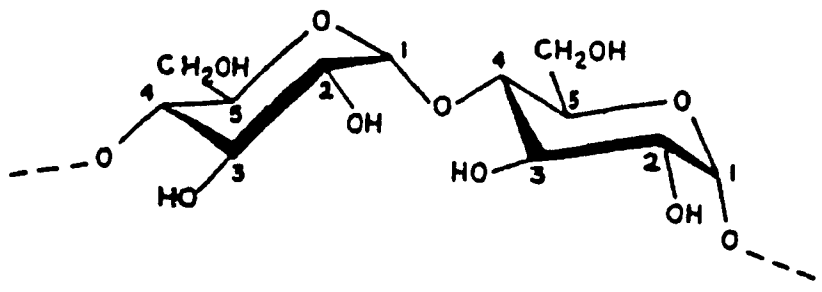
As a consequence of the C1 conformation of the glucopyranose units, all the secondary hydroxyl groups are situated on one of the two edges of the ring, whereas all the primary ones are placed on the other edge. The cavity of the cyclodextrin is lined by the hydrogen atoms and the glycosidic oxygen bridges respectively. Therefore, the interiors of the cavities of cyclodextrins are relatively apolar compared to water.

Figure 1. The structure of α-cyclodextrin (a) schematic diagram of two glucopyranose units of a cyclodextrin molecule illustrating details of the α-(1,4) glycosidic linkage[1] (b).

(a)



(b)



1.2 HOST GUEST INTERACTIONS

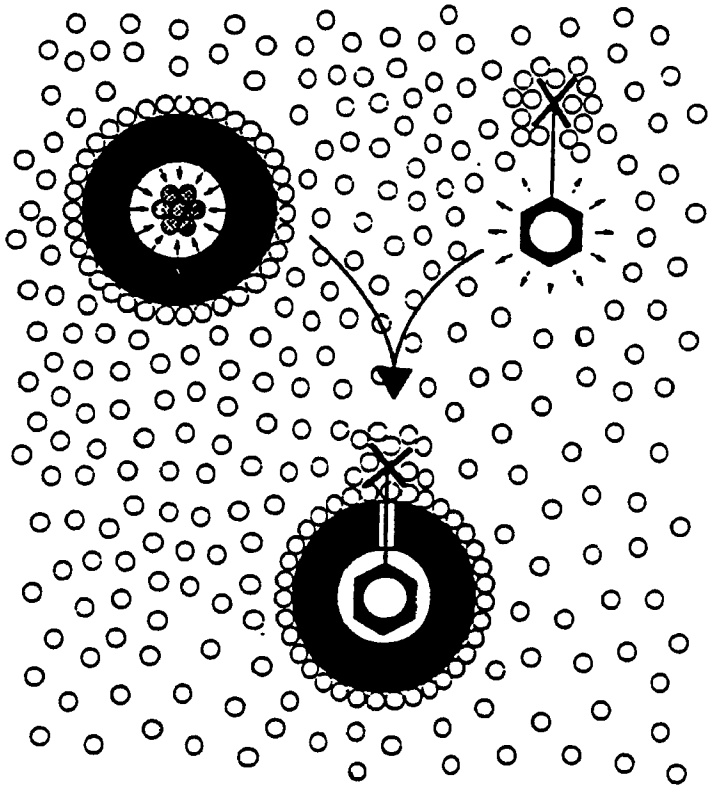
"THE INCLUSION COMPOUNDS"

Because of the cavities and their relative hydrophobicity, CDs can form inclusion complexes.[1,2] Cyclodextrins are able to interact with a great variety of ionic and molecular species and the resulting inclusion compounds belong to the type of "host-guest" complexes.

The extent of the complex formation depends on both the size, which must be compatible with the dimensions of the cavity of CD, and the polarity of the guest molecule.[2] The included molecules (guests) are oriented in such a way as to achieve the maximum contact between the hydrophobic part of the guest and the apolar cyclodextrin cavity. The hydrophilic part of the guest molecule remains at the outer face of the complex to ensure maximum contact with both the solvent and the hydroxyl groups of the CD, Figure 2.

It has been found that only water is suitable for the preparation of the complexes, because from other solvents, the solvent complexes may crystallize or a ternary complex (CD . solute . solvent) may be formed.

Figure 2. Schematic representation of the formation of cyclodextrin inclusion complexes.



The most direct evidence for the inclusion of a guest into the cyclodextrin cavity in solution has been obtained by H^1-NMR spectroscopy.[1] The H-3 and H-5 atoms of the CD, which are directly toward the interior of the cavity showed a significant upfield shift upon addition of substituted benzoic acids to CD solutions in D_2O. On the other hand, the H-1, H-2 and H-4 atoms located on the exterior of the cavity showed only a marginal upfield shift. The large upfield shift for the H-3 and H-5 atoms ascribed to anisotropic shielding effect of the benzene rings of the benzoic acids, strongly suggests binding in the cyclodextrin cavity. The inclusion compounds usually have a 1:1 stoichiometry[3] but more recently, a binding of 2:1 CD-substrate molecules has also been characterized.[4] The strength to which complexation takes place is often expressed as a dissociation constant K_d (=1/formation constant).

The methods used for determining the dissociation constant (K_d) are mainly based on the properties of solutions of the substrate and CD. The concentration of one of the reactants or product is followed (directly or indirectly) by a suitable analytical method. Usually the potentiometric, extraction, NMR and kinetic methods can be used to measure concentration and hence K_d. The most widely-used method of determining such constants has been using UV-visible absorption spectroscopy, where significant changes with respect to the absorption and wave length maximum may take

place upon complexation.

With the kinetic method the saturation effect of [CD] on the reaction rate may be used to determine K_d.[5] Also, as will be discussed later, inhibition kinetics were used in the present study to measure the strength of the binding of several substrates.

1.3 THE EFFECTS OF CYCLODEXTRINS ON REACTIVITY

As a consequence of their abilities to form inclusion complexes, CDs can show significant catalytic or inhibitory effects when added to a variety of reactions.[1,2,5]

The catalytic effects of CDs can be classified into two types, depending on whether or not the cyclodextrin forms a covalently bonded intermediate[3]. Consider the situation shown in Scheme 1, where

$$S \xrightarrow{k_u} P$$

$$S + CD \underset{K_d}{\rightleftharpoons} S.CD \xrightarrow{k_c} P$$

Scheme 1

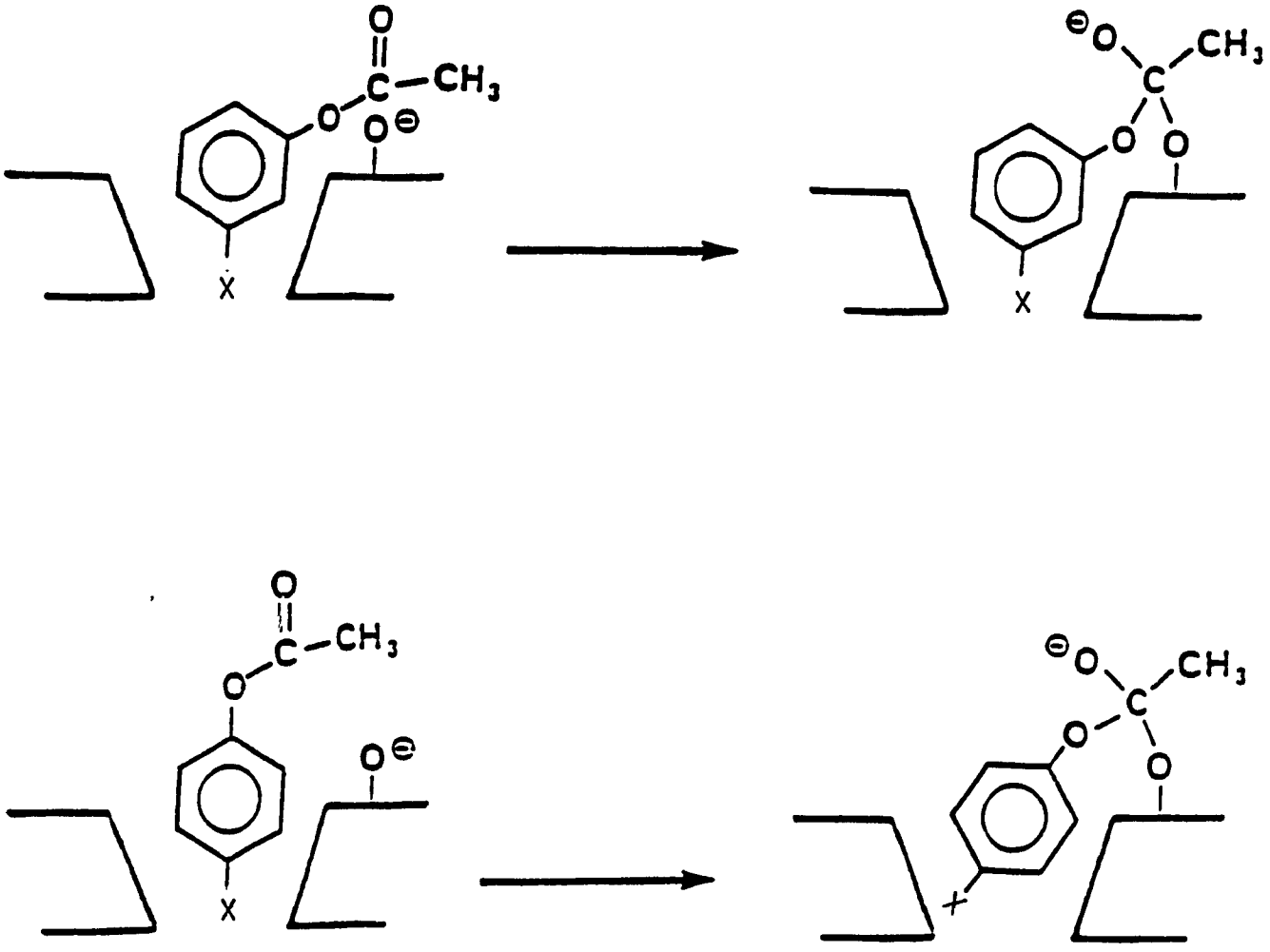
under these conditions, and assuming [CD] > > [S],

$$k_{obs} = (k_u K_d + k_c[CD]) / (K_d + [CD]) \qquad \text{------ (1)}$$

Equation 1 describes saturation kinetics[1,7] since at high [CD] k^{obs} approaches the limiting value of k_c. Note that if $k_c > k_u$

the effect of CD is catalytic, whereas if $k_u > k_c$ its effect is inhibitory. k_u is the rate constant in the absence of [CD], K_d is the dissociation constant of S.CD complex, and k_c is the rate constant for the complex.

An example of covalent catalysis is the cleavage of phenyl esters in the presence of α or ß CDs in basic solution.[1,3,5] Studies indicated that the CD attacks the carbonyl group of the substrate nucleophilically with its deprotonated secondary hydroxyl groups acting as the active species. It was suggested that the meta substituents on the phenyl ring fix the ester group in closer proximity to the secondary hydroxyl group of the cyclodextrin than do para substituents, (Scheme 2).



Scheme 2

In a more recent study[5,6] it has been observed that for two series of esters (acetate, propanoate, butanoate, pentanoate and hexanoate) in a basic buffer containing CD, the m-nitro derivatives undergo more efficient cleavage than their p-nitro isomers. Moreover, the m-nitro isomers react via aryl group inclusion, whereas the p-nitro compounds bind through their alkyl groups in the transition state.[6] Consequently it was concluded that the position of the substituent largely governs the selectivity of CDs towards different ester substrates. In another work in this laboratory, it has been shown that CDs accelerate the rates of hydrolysis of aspirin derivatives in aqueous base via covalent catalysis and similar substituent effects were found.[7]

In general, most CD-catalyzed reactions show modest rate accelerations (1-300). More spectacular values have been obtained by modifying the substrates so that they bind more strongly in the transition state. In their study Breslow et al[8,9] synthesized various ferrocene acrylate esters which exhibit accelerations up to 6 million. In addition the chirality of the CD molecule leads to substantial enantio selctivity, with a ratio of 65 in favour of one mirror image isomer over the other.[9]

In many CD-catalyzed reactions there are no covalent interactions between the substrate and the cyclodextrin, a situation referred to as non-covalent catalysis.[1] Such catalysis by CDs may be the result of either a microsolvent effect or of a conformational effect.

The microsolvent effect operates due to the apolar character of the CD cavity. In this case the apolar cavity of the CD provides a reaction medium different from the bulk solvent where the substrate is slightly more reactive. The conformational effects are the result of the geometric requirements of inclusion.

An example of such non-covalent catalysis is the decarboxylation of β-keto acids.[1] Anionic decarboxylations are extremely solvent dependent, proceeding much faster in solvents of low dielectric constant. Therefore, acceleration of these reactions by CDs is attributable to the microsolvent effect since the interior of the CD cavity provides an apolar or ether-like atmosphere. Recently, Tee and Bennett[10] found that the bromination of phenols in the presence of α-CD is subject to non-covalent catalysis. This work will be discussed more fully later.

Regardless of the type of catalysis involved in a reaction, the substrate reacts in the form of an inclusion complex. This means that the reaction will exhibit saturation kinetics[1,2], as mentioned earlier. Furthermore, inhibition must occur if an inert molecule is added which can compete with the substrate for binding site of the CD.[3,5] Both phenomena have been studied in many CD catalyzed reactions. This indicates that as CDs show the behaviour typical of enzymatic reactions, they serve as good enzyme models for the examination of effect of the formation of the enzyme-substrate complex on the enzyme catalyzed reactions.

CHAPTER 2

EFFECTS OF α-CYCLODEXTRIN ON THE RATES OF BROMINATION REACTIONS

2.1 "BROMINATION OF ANISOLE" A BRIEF REVIEW

In an earlier work done by Breslow and Campbell[11], it was revealed that by using appropriate amounts of α-CD, the para/ortho product ratio for the chlorination of anisole by hypochlorous acid can be raised significantly.

In order to see the effects CDs may have on other reactions, Tee and Bennett[12] studied the effect of α-CD on the kinetics of bromination of anisole and p-methyl anisole. (All the bromination reactions had been carried out in excess of bromide ion concentration).[13] The overall effect of α-CD was found to substantially retard the rate of bromination of both anisole and p-methylanisole. It was concluded that α-CD reduces the rate of bromination of p-metylanisole due to the complexation of tribromide ion and, to a lesser extent, of bromine and the substrate itself. The only important bromination pathway seems to be that involving free substrate and free bromine.

In the case of anisole, however, the extent of rate inhibition was much less than expected from the measured dissociation constants of the inclusion complexes formed. It was also observed that at high CD concentration the pseudo-first-order rate constants for the disappearance of bromine

increase monotonically with anisole concentration. This indicates that the transition state for this process contains anisole. Also, this eliminates the possibility of rate-limiting dissociation of the CD-bromine or CD-tribromide ion complexes. Experiments done at varying pHs did not show any reaction occurring via the hypohalite ester of α-CD unlike the chlorination of anisole.[11]

It was then concluded that apart from the normal course of bromination reaction, another pathway is also involved which becomes important only at higher concentrations of α-CD.

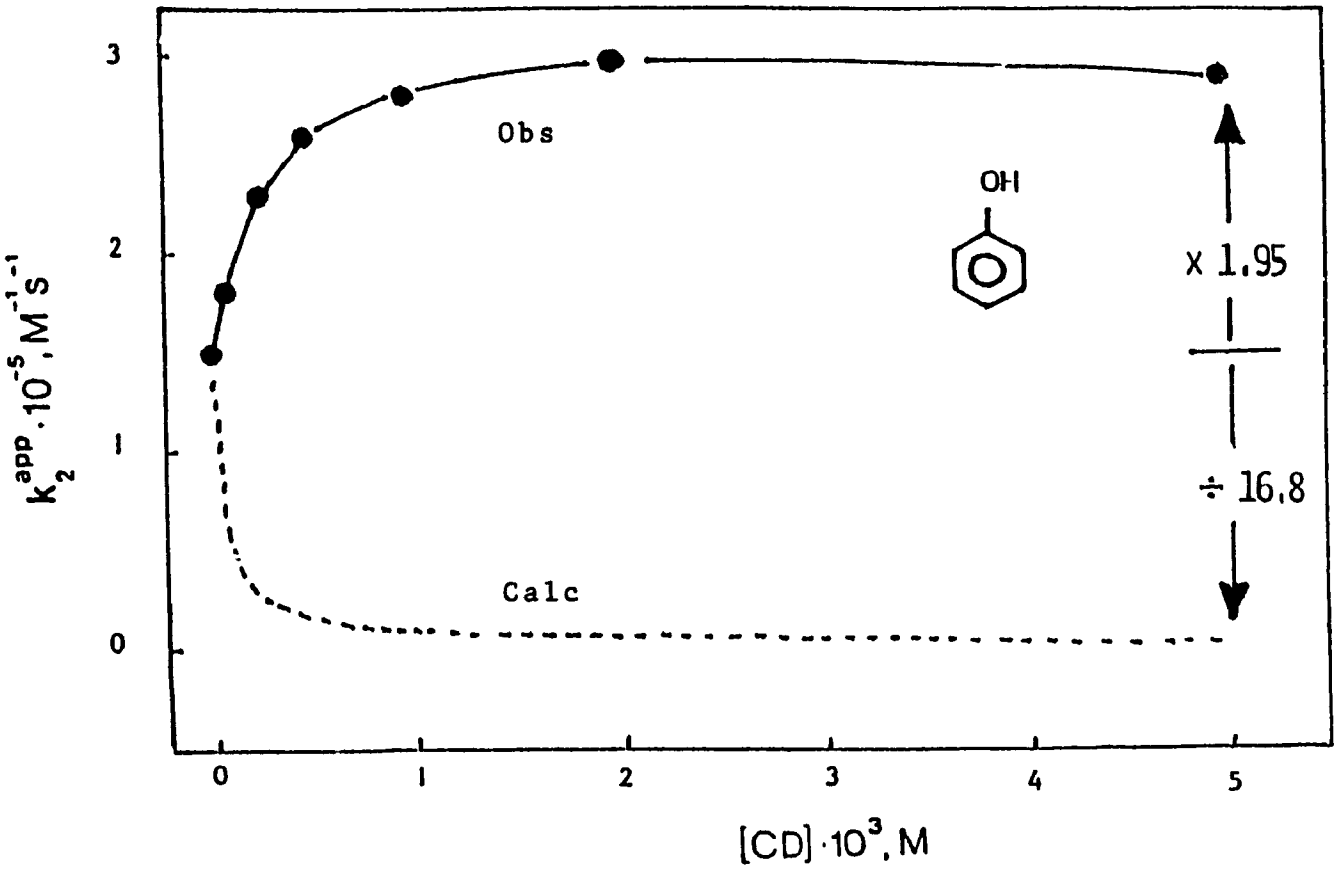
2.2 "PHENOLS AND PHENOXIDE IONS"

Phenols undergo bromination reactions both in the parent form and the anionic form, depending on the pH of the reaction medium.[14,15] The aqueous bromination of phenols has been extensively studied in the past few years.[10,16,17]

Recently Tee and Bennett studied the rates of bromination of several phenols and phenoxides in the presence of α-CD.[10] These species form host-guest complexes with α-CD in which the meta and para positions of the phenol reside within the hydrophobic cavity of the cyclodextrin host.[1,3] Since bromine also forms a complex with CD[11], it was expected that CD would exert significant effects on the normal course of phenol bromination.

It was found that bromination kinetics in the presence of excess of Br^- involves five important equilibria i.e. tribromide ion formation[13,14] and the complexations of CD with tribromide ion[12], bromine[11], bromide ion[18] and the phenol.[11] Taking into account all the above encapsulations, the apparent second-order rate constants (k_2^{app}) were obtained for the bromination of phenol as a function of α-CD concentration. It was observed that the rate shows slight acceleration with increasing catalyst concentration. If bromination proceeds solely via both free reactants, k_2^{app} should decrease dramatically with increasing α-CD. Figure 3 shows this situation where the calculated second-order rate constant k_2^{cal} is graphically compared to the observed rate constant , as a function of α-CD concentration.

Figure 3. Variation of k_2^{app}, $M^{-1}s^{-1}$ for the bromination of phenol with total concentration of α-CD.[10]



The discrepancy between the observed and calculated rate constants is of the order of 32.7 at the maximum CD concentration. Therefore with rate acceleration being the case, it appears that there exists a bromination pathway involving α-CD.

Based on the successful results obtained for phenol, a series of mono and di-substituted phenols and phenoxides were also studied in the same manner. Analysis of the data for the above compounds provided rate constants from which it was concluded that the substrates react via a catalytic pathway involving complexed bromine reacting with free substrate. In part this conclusion was based on the observation that the substituents' effects are virtually the same for the catalyzed and normal bromination of phenols. Also for phenoxide ions both reactions are diffusion controlled, the rate slightly higher for the CD-catalyzed reaction.

2.3 THE DISSOCIATION CONSTANTS OF THE CD-SUBSTRATE COMPLEXES

GENERAL INTRODUCTION

The complexity of the catalytic reactions arises due to the inclusion compounds which are formed as a result of the binding of CDs with the various species involved in that particular reaction. The thermodynamic stability of a CD complex is generally expressed in terms of the formation constant (K_f) or dissociation constant ($K_d = 1/K_f$). The constants for CD-Br_2[11], CD-Br^- and CD-Br_3^-[10] were already known.

To find out the dissociation constants of some of the CD-substrate complexes, we made use of the inhibitory effects the formation of these complexes have on the base hydrolyses of m-nitro-phenyl acetate in the presence of α-CD.[5] Gradual rate retardations are seen with the increase in the concentration of the inhibitors. Analysis of the data gives the values of inhibition constants, which are then used as the dissociation constants for the CD-substrate complexes involved in the catalytic bromination reactions.

2.4 OBJECTIVES

The earlier work[10] done in this laboratory concerning the effects of α-CD on the bromination of phenols unveiled an important behaviour of α-CD as a bromination catalyst.

The results of the above work lead one to raise further questions as to how, and in what way, the reactions of other organic compounds could be influenced by α-CD. The present study was undertaken to investigate how the rates of bromination reactions of some other phenols, various salicylic acids and other aromatic and heteroaromatic acids are altered by α-CD. The contribution to the catalysis by substituents' effects is also further investigated.

It is hoped that by carrying out this work, a clearer picture of cyclodextrins' behaviour would appear, which might help in better understanding the future problems in the field of cyclodextrin research.

CHAPTER 3

RESULTS

The bromination kinetics of various compounds involved in this study in aqueous solutions containing α-CD have been carried out by using UV-visible spectrophotometry and the stopped flow-technique.[15,16] Since α-CD forms important complexes with the compounds involved in various equilibria, it is necessary to review these equilibria[10], before presenting the present results.

3.1 EQUILIBRIA[10,12]

Bromination reactions in aqueous solutions are most conveniently studied by using an excess of bromide ion.[13] The decrease in absorbance due to the tribromide ion is then monitored. This ion is formed in a fast equilibrium.[20]

$$Br_3^- \rightleftharpoons Br_2 + Br^- \qquad \text{------ (2)}$$

$$K = [Br_2]\,[Br^-] / [Br_3^-] = 0.0562\ M$$

For a large excess Of Br^- over Br_2, the fraction of free bromine is given by:

$$f_B = K / (K + [Br^-]) \qquad \text{------ (3)}$$

The dissociation constant (K_I) was determined by Wojcik and Rohrbach[18] for the complex formed between α-CD and bromide ion:

$$CD.Br^- \rightleftharpoons CD + Br^- \quad K_I = 0.286\ M \qquad \text{------ (4)}$$

This value shows only weak complexation of Br^- with CD, but it cannot be ignored since the concentration of Br^- in the present work is high. The amount of free CD available for the complexation of other species is then given by:

$$[CD] = [CD]_t\ K_I\ /\ K_I + [Br^-] \qquad \text{------ (5)}$$

Where $[CD]_t$ is the total CD concentration. Breslow and Campbell's [11] work proved a strong binding of α-CD with bromine.

$$Br_2 \cdot CD \overset{K_B}{\rightleftharpoons} Br_2 + CD \qquad \text{------ (6)}$$

$$K_B = [Br_2][CD]/[Br_2.CD] = 2.1\ mM$$

Under our experimental conditions this complexation does not significantly effect the concentration of α-CD, since the concentration of Br_2 used is < 0.05 mM. However, it does contribute to the reduction in the free bromine concentration.

The most noticeable inclusion involving α-CD was found to be that involving the tribromide ion[10]:

$$Br_3^- \cdot CD \underset{}{\overset{K_T}{\rightleftharpoons}} Br_3^- + CD \qquad \text{------ (7)}$$

$$K_T = [Br_3^-][CD]/[Br_3^-.CD] = 0.17 \text{ mM}$$

The low value of K_T indicates a 10-fold stronger binding than that of bromine, and this strong complexation directly affects the concentration of free bromine under the experimental conditions. As a result of these complexations the amount of free bromine in solution is reduced. Total bromine is then

$$[Br_2]_t = [Br_2] + [Br_3^-] + [Br_2]_C + [Br_3^-]_c$$

where the subscript c indicates complexed species. The amount of free bromine (f_B) then becomes:

$$f_B = KK_BK_T/(K_BK_T\ (K+[Br^-]) + [CD]\ (KK_T+K_B[Br^-])) \qquad \text{------ (8)}$$

The formation of substrate-CD complexes is easily corrected for by taking the fraction of free substrate as:

$$f_s = [S]/[S]_t = K_s\ /\ (K_s + [CD]) \qquad \text{------ (9)}$$

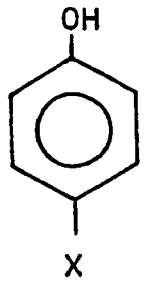
where $[S]_t$ is the total substrate and K_s is the dissociation constant of the CD-substrate complex.

3.2 BROMINATION KINETICS IN THE PRESENCE OF α-CD

a: PHENOLS AND SALICYLATE IONS

The rates of bromination of three phenols (1a, 1b, 1d) at pH 1, and three substituted salicylic acids (1e, 1f, 1g) at pH 5, have been measured both in the absence of and presence of varying amounts of α-CD.

PHENOLS

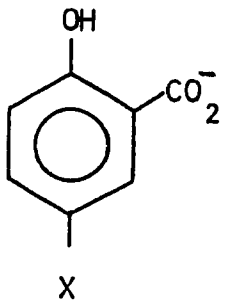


1a; x = F

1b; x = Cl

1d; x = I

SALICYLATES



1e; x = Br

1f; x = SO_3^-

1g; x = NO_2

Due to the advantages of the formation of Br_3^-, all the bromination kinetics have been studied in the presence of excess of Br^- ion[13]. With a 10-fold excess of substrate over bromine, good pseudo-first-order rate constants (k_1^{obs}) were obtained for the disappearance of bromine.

For phenols [14,21,22] and salicylate ions[23] the values of k_1^{Obs} were found to be a direct function of the substrate concentration, showing an overall second-order kinetics; first order in substrate and first order in bromine. The apparent second-order rate constants (k_2^{app}) are thus derived from the values of first-order rate constant by taking into account the substrate concentration.

The present results for the uncatalyzed bromination of salicylic acids show good agreement with the results of Iyengar[23] where k_2^{obs} = 4.98×10^6 $M^{-1}s^{-1}$; 0.958×10^5 $M^{-1}s^{-1}$ and 2.13×10^4 $M^{-1}s^{-1}$ for 5-Br, 5-SO_3^- and 5-NO_2 salicylic acids at pHs 5, 4.76 and 4.71 respectively. For the uncatalyzed bromination reactions:

$$S + Br_2 \xrightarrow{k_2} P$$

in the presence of excess of Br^- the apparent rate constant k_2^{app} is reduced relative to the actual rate constant (k_2) due to the formation of Br_3^- (see eq.2). The rate expression is:

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

$$\text{therefore } k_2^{app} = k_2 f_B \qquad \text{------ (10)}$$

where $f_B = [Br_2]/[Br_2]_t$ is the fraction of free bromine. Therefore the observed bromination rate constant may be expressed as:

$$k_2^{obs} = k_2^{app} / f_B \qquad \text{------ (11)}$$

In the presence of α-CD k_2^{app} should decrease even more due to reductions in the free bromine and free substrate; here f_B must take account of the additional encapsulations involving bromine species (see eq.8). To also consider substrate encapsulation however, the rate constant must be redefined, taking into account the free substrate. Then

$$k_2^{app} = k_2 f_s f_B \qquad \text{------ (12)}$$

where $f_s = [S]/[S]_t = K_s / K_s + [CD]$

This rate constant accounts for all the known complexations.

Table I shows the results obtained for the bromination of p-chloro phenol (1-b) as a function of α-CD concentration at pH 1. It can be seen that k_2^{app} is substantially reduced in a manner consistent with the complexation of Br_3^-, Br_2 and the p-chloro phenol, although the effect of the first of these is dominant.[10]

As [CD] is raised from 0 to 5 mM, the observed value of k_2^{app} decreases by a factor of 3.28. This decrease is smaller than the factor of 32 which should arise due to the complexation with CD of Br_3^-, Br_2 and the phenol. If

bromination occurs only via both free reactants, k_2^{app} should decrease considerably with increasing CD concentration. Figure 4 shows the calculated second-order rate constant in comparison with the observed second-order rate constant as a function of α-CD concentration. It appears that there exists an additional phenomenon which becomes important as the concentration of CD is increased.

For the calculated values, k_2^{app} rapidly declines at low CD concentrations and then levels off due to saturation of the complexation equilibria. For the observed values, somewhat similar picture is exhibited, except that the rate constants are much higher than anticipated. It appears that there exists a bromination pathway involving α-CD.

Figure 4. The observed and calculated apparent second-order rate constants as a function of $[\alpha\text{-CD}]_t$, for the bromination data of p-chloro phenol.

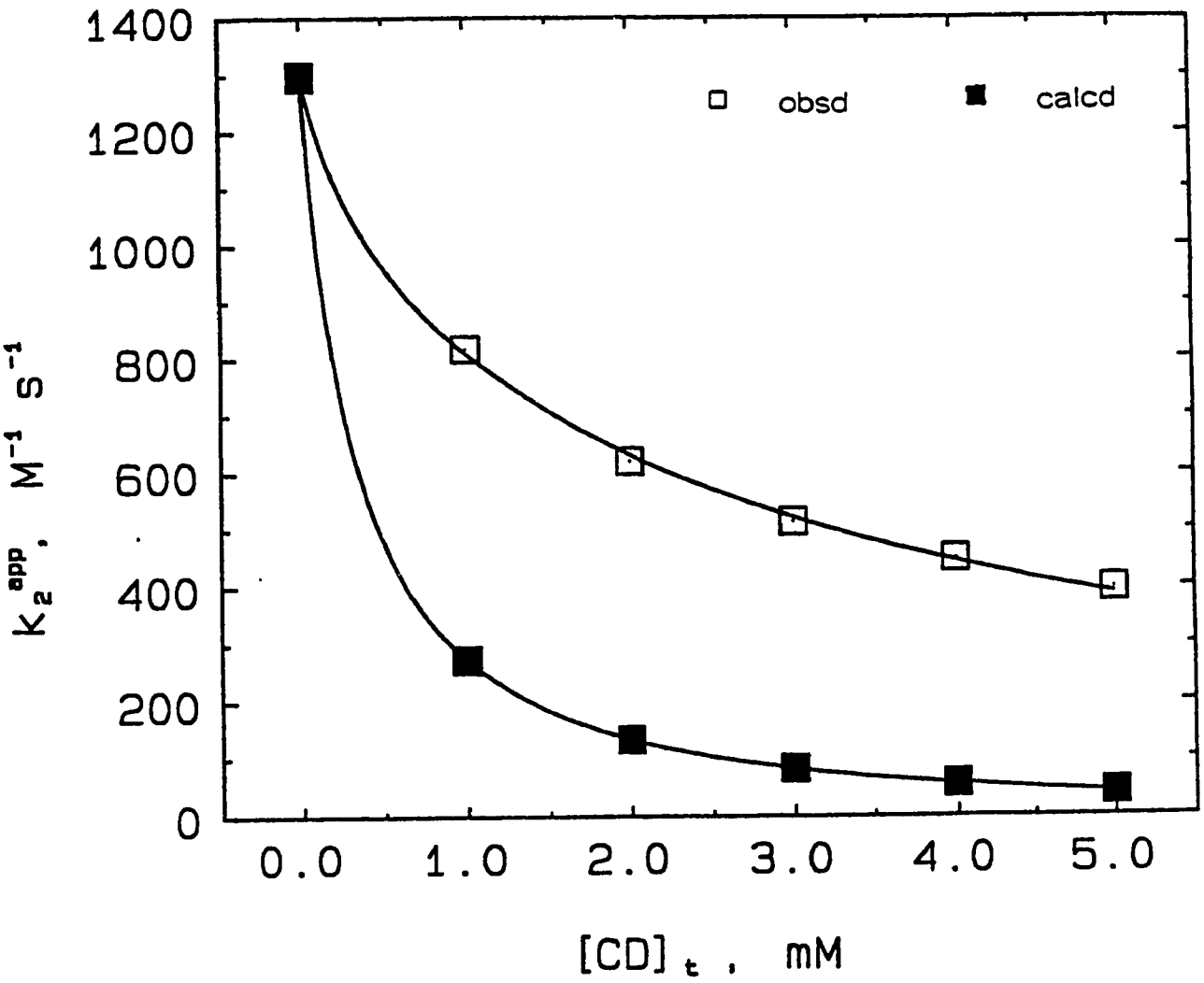


Table I. The observed and calculated apparent second-order rate constants (k_2^{app}, $M^{-1}s^{-1}$) for the bromination of p-chloro phenol (1b) as a function of α-CD concentration.

$[\alpha\text{-CD}]_t$, mM	k_2^{app}, $M^{-1}s^{-1}$	
	obs	Cal[a]
0	1300	1296
1	818	273
2	620	133
3	513	81.7
4	449	55.5
5	396	40.6

[a] The calculated values are based on the reaction between the free substrate and free bromine (eq.12).

Such behaviour has also been observed for other phenols and salicylates: p- fluoro phenol, p-bromophenol, p-iodo phenol, 5-bromo salicylic acid, 5-sulfo salicylic acid and 5-nitro salicylic acid. The apparent second-order rate constants for these compounds are given in Table AI (See Appendix).

The existence of an additional process is consistent with the bromination data obtained previously for various mono and di-substituted phenols.[10] For analysis of the data we consider a CD-catalyzed pathway involving substrate, bromine and one molecule of CD:

$$S + Br_2 + CD \xrightarrow{k_3} P$$

If such a process is involved, k_2^{app} has contributions from the normal bromination and this additional process:

$$k_2^{app} = (k_2 + k_3[CD])\ f_s f_B \qquad \text{------ (13)}$$

This equation has a nonlinear dependence on [CD] because of the forms of f_s and f_B (eq.8 and 9) which also involve [CD]. Equation (13) is then rearranged to define a constant (k_2^*) with a linear dependence on [CD]:

$$k_2^* = k_2^{app} / f_s f_B = k_2 + k_3[CD] \qquad \text{------ (14)}$$

As an example Figure 5 shows the results obtained from the

Figure 5. Plot of k_2^* vs $[CD]_{corr}$ for the data shown in Table II, based on eq.14. It is linear with a slope of $k_3 = 7.33 \times 10^8\ M^{-2}s^{-1}$. Note that [CD] is corrected through the use of eq.5.

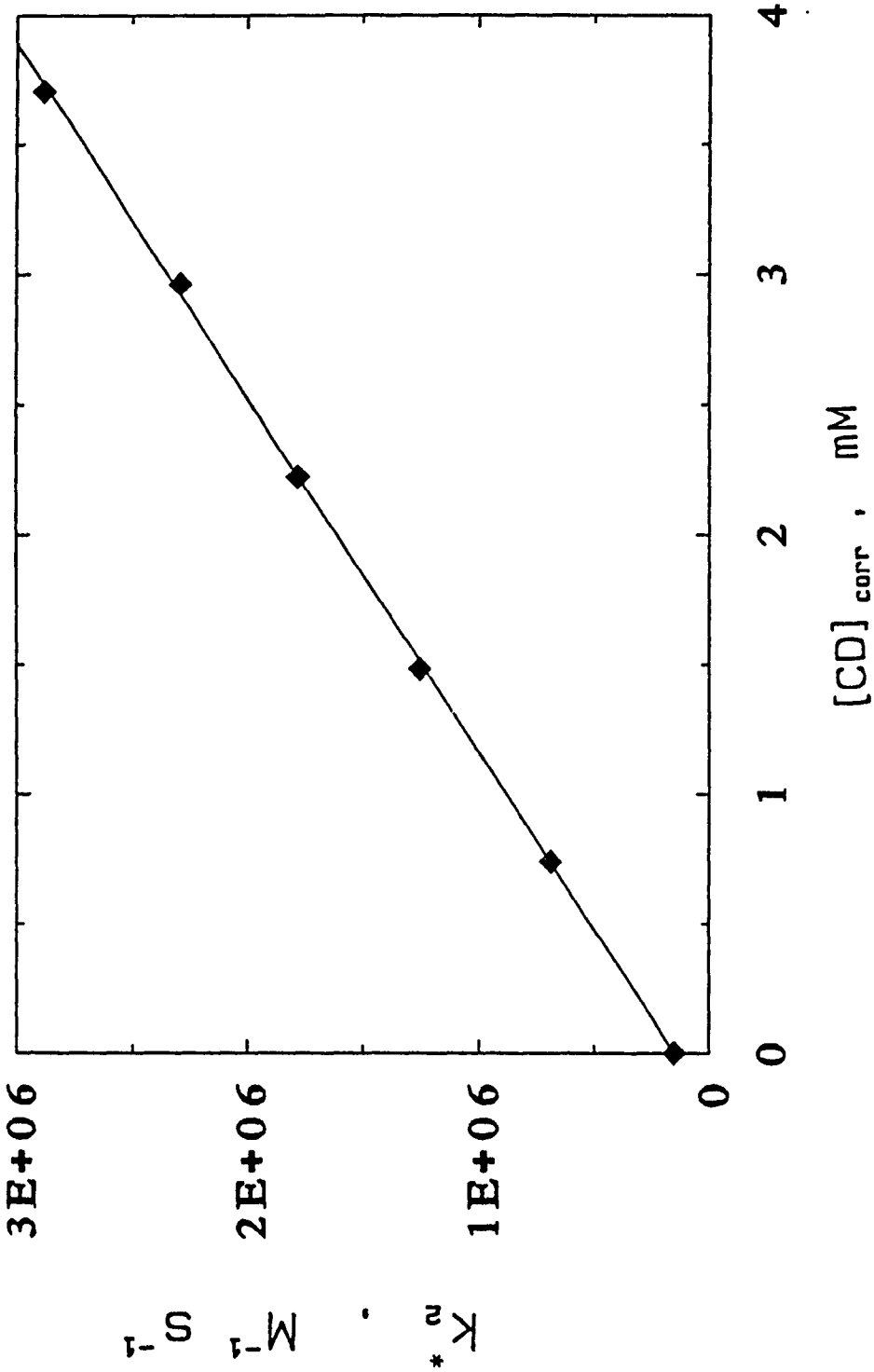


Table II. Rate constants for the aqueous bromination of 5-bromo salicylic acid (1.d) as a function of α-CD[a] concentration at pH 5.

$[CD]_t$ mM	$[CD]_{corr}$ mM	$k_2^{app}.10^4$ $M^{-1}s^{-1}$	$k_2^*.10^6$ $M^{-1}s^{-1}$
0	0	5.40	0.1501
1	0.741	5.44	0.688
2	1.48	5.0	1.27
3	2.22	4.42	1.78
4	2.96	3.96	2.29
5	3.71	3.69	2.89

[a] These data are plotted in Figure 5.

aqueous bromination of 5-bromo salicylic acid at pH 5, as a function of α-CD concentration (Table II), treated according to eq.14. The resulting plot is quite linear, with a good correlation (r =0.99986) and a slope of $k_3 = 7.33 \times 10^8$ $M^{-2}s^{-1}$. The good linearity indicates that only <u>one</u> molecule of α-CD is involved in the transition state of the catalyzed bromination pathway.[10]

Similar straight lines ($r > 0.9990$) have been obtained for other phenols and salicylates. The slopes of plots give the values of third order rate constants (k_3) for catalysis. Table III summarizes both the uncatalyzed and catalyzed rate constants for the above compounds. Detailed discussion of these results is presented later.

Table III. Rate constants for the aqueous bromination of phenols and salicylate anions in the presence of α-CD[a].

Substrate	No.	k_2 $M^{-1}s^{-1}$	k_3 $M^{-2}s^{-1}$
Phenol			
4-F	1-a	4.35×10^3	1.12×10^7
4-Cl	1-b	3.60×10^3	8.40×10^6
4-Br[b]	1-c	3.92×10^3	8.54×10^6
4-I	1-d	5.53×10^3	1.90×10^7
Salicylate			
5-Br	1-e	1.50×10^5	7.33×10^8
5-SO_3^-	1-f	1.10×10^5	1.83×10^8
5-NO_2	1-g	1.61×10^4	2.40×10^7

[a] For phenols the bromination is at pH 1, where the reaction is on the undissociated form.[10] For salicylates, reaction is at pH 5, on the mono anions.[23]

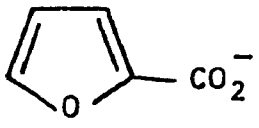
[b] For this compound, data is taken from the literature.

b: AROMATIC AND HETEROAROMATIC CARBOXYLATE IONS

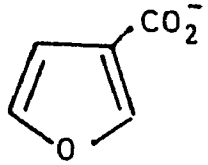
Molecular bromine reacts with the undissociated form of activated aromatic acids at lower pH and carboxylate ions at higher pH, depending on the pK_a of the acids. For example Iyengar[23] studied the kinetics of bromination of some o- and p- hydroxybenzoic acids in aqueous buffers in the pH range of 0-7. At the same time, two methoxy compounds, o-anisic acid and p-anisic acid were also studied. All of these substrates exhibit second-order kinetics: First order in substrate and first order in bromine, at fixed pH.

In the present work, rate constants for the aqueous bromination of some aromatic and heteroaromatic acids (2a-2g) have been measured at pH 5, both in the presence of and absence of α-CD. In the presence of a large excess of substrate, pseudo first-order rate constants were obtained for the disappearance of bromine.

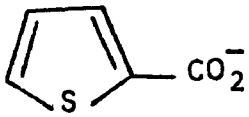
Measurements were made at pH 5, so as to avoid any reaction of the undissociated form of the acid, and hence eliminating the pH dependence factor.



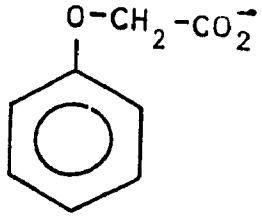
2a 2-furoate



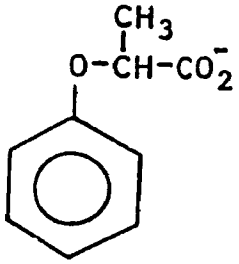
2b 3-furoate



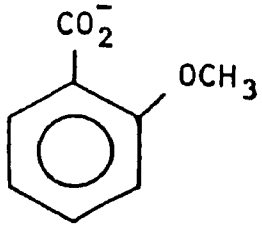
2c 2-Thiophene carboxylate



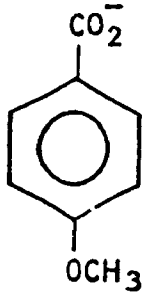
2d Phenoxy acetate



2e 2-Phenoxy propionate



2f 2-Anisate



2g 4-Anisate

Rate constants, at various [CD], for the above compounds are shown in Table A-II. The present results for the bromination of compounds (2f) and (2g) agree reasonably well with the results obtained previously[23], where k_2^{obs} for (2f) and (2g) are 8440 $M^{-1}s^{-1}$ at pH 5.08 and 234 $M^{-1}s^{-1}$ at pH 5.04 respectively. (at [α-CD]=0).

Similar to the phenols, the rate constants for these compounds decrease as a function of [α-CD]. (e.g. Figure 6). A rapid decline in rate occurs at low CD concentration which eventually levels off due to saturation of the complexation equilibria. For each of compounds 2a-2g, the observed values of k_2^{app} are much bigger than the expected values of k_2^{app} calculated from eq.12. An example of the variation of rate with [CD] is shown in Figure 6. The value of k_2^{app} decreases with increasing [CD] until at 5mM, it has gone down by a factor of 6. Whereas the expected value of k_2^{app} (from eq.12) is decreased by a factor of 17 (Table IV).

The variations of k_2^{app} With $[CD]_t$ have also been determined for six other carboxylic acids.

Figure 6. Variation of the observed and calculated rate constants with $[\alpha\text{-CD}]_t$, of 2-furoate, at pH 5.

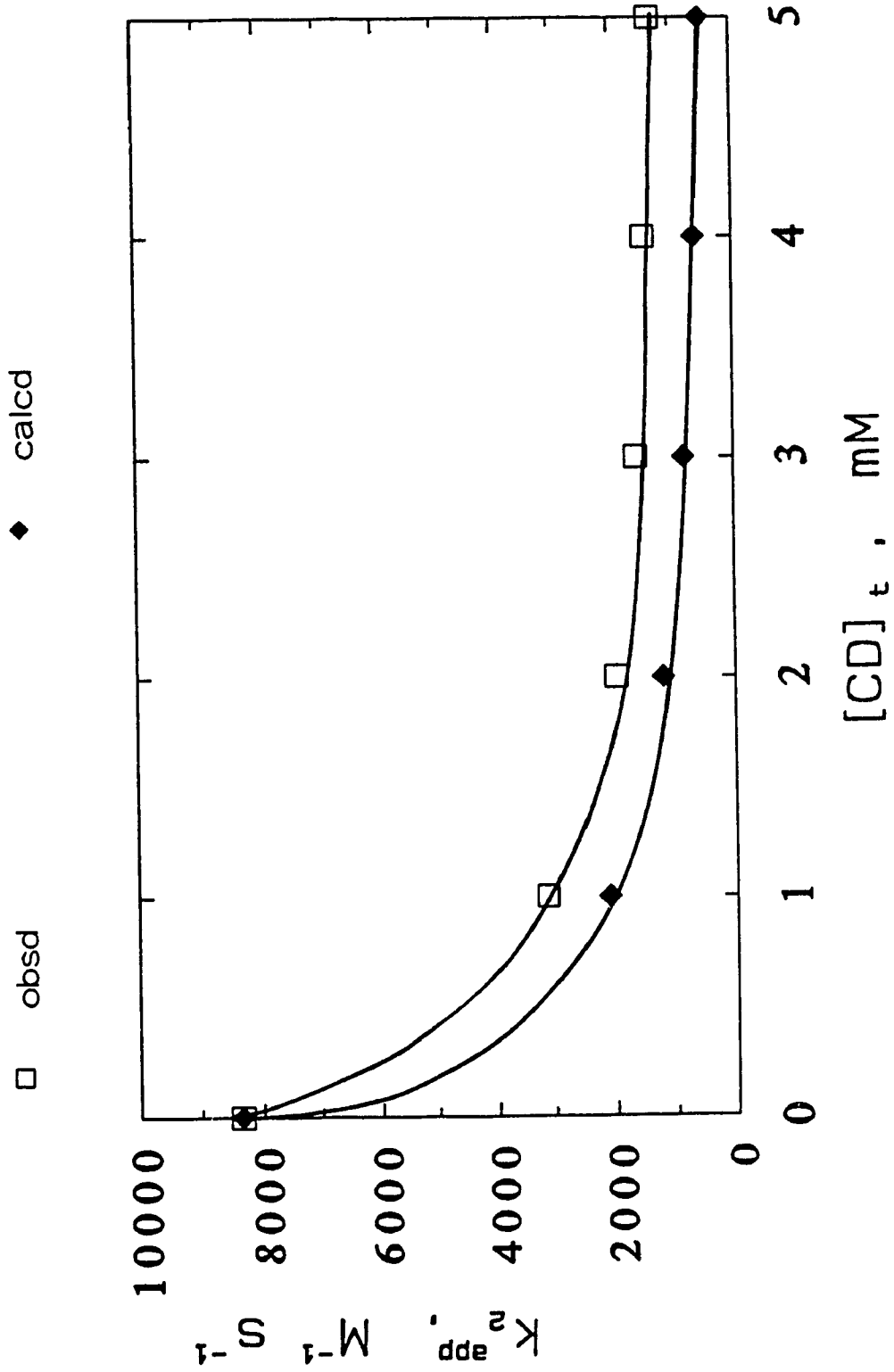


Table IV. The observed and calculated second-order rate constants for the bromination of 2-furoate (2a) as a function of α-CD concentration.

$[\alpha\text{-CD}]_t$, mM	k_2^{app}, $M^{-1}s^{-1}$	
	obs	Cal
0	8333	8329
1	3133	2102
2	1971	1191
3	1611	824
4	1453	627
5	1331	503

(2b-2g, Table AII), at pH 5 where the reaction occurs via the anion of the substrate. In each case the rate of reaction decreases, but in no case is the decrease as large as that required by eq.12. Therefore there is a CD catalyzed pathway that partially compensates for the suppressionof normal reaction of bromine with the aromatic acid.

Like phenols, the plots of k_2^* vs [CD] for furoates '2a' and '2b' (Figure 7) are linear, indicating the involvement of one CD in bromination.[10] The slopes of these plots give third-order rate constants (k_3 $M^{-2}s^{-1}$) for the catalytic bromination in the presence of α-CD. The results for all of the aromatic acids 2a-2g are presented in Table VI, together with the values of observed second-order rate constants at zero [CD].

Figure 7. Plots of k_2^* vs $[CD]_{corr}$ for 2- and 3-furoates (2a and 2b) for the data shown in Table V.

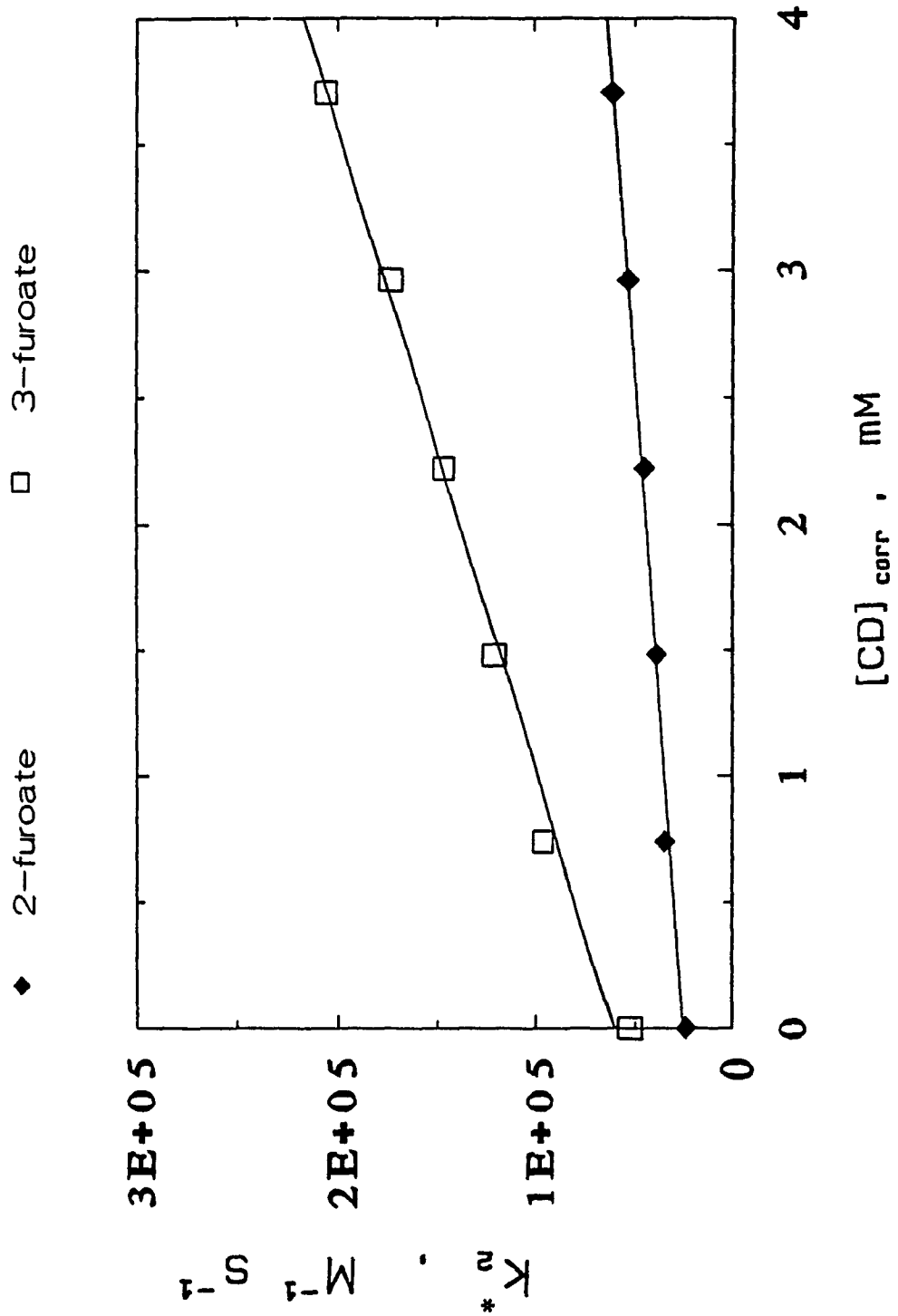


Table V. The resultant values of k_2^* and $[CD]_{corr}$ for substrates 2a and 2b as treated by eq.14.

$[CD]_t$	$[CD]_{corr}$	$k_2^{app}.10^3$ $M^{-1}s^{-1}$		$k_2^* . 10^4$	
mM	mM	2a	2b	2a	2b
0	0	8.33	18.8	2.32	5.23
1	0.741	3.13	8.73	3.45	9.60
2	1.48	1.97	6.24	3.84	11.8
3	2.22	1.61	5.24	4.53	14.7
4	2.96	1.45	4.73	5.37	17.7
5	3.71	1.33	4.53	6.13	20.6

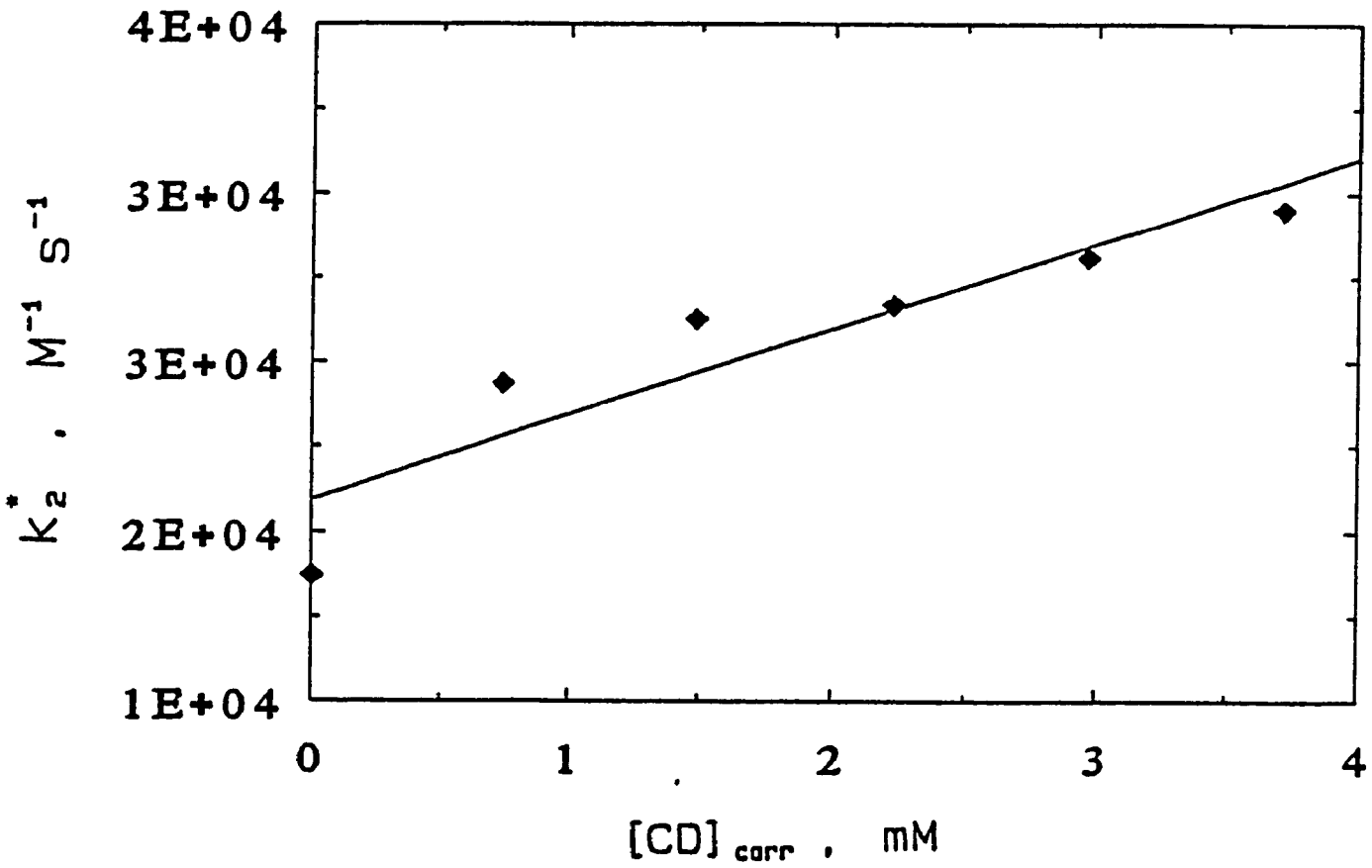
For the compounds other than the furoates, however, the same plot, k_2^* vs [CD] shows a slightly different picture. An example of such a plot is shown in Figure 8. Such curved plots showing significant curvature at low [α-CD] have also been found for four other carboxylates: 2c, 2e, 2f and 2g. This nonlinearity seems to arise due to the insufficient or poor 1:1 binding of the substrate with α-CD at low concentrations of α-CD. This behaviour of carboxylate ions will be discussed in the next sections.

Table VI. Rate constants for the aqueous bromination of carboxylate ions[a].

Carboxylate	k_2^{obs}, $M^{-1}s^{-1}$	k_3, $M^{-2}s^{-1}$
2-Furoate	2.32×10^4	9.85×10^6
3-Furoate	5.23×10^4	3.96×10^7
2-Thiophene	1345	2.85×10^5
Phenoxy acetate	1.56×10^4	3.79×10^6
2-Phenoxy propionate	2.95×10^4	5.39×10^6
2-Anisate	1.96×10^4	8.95×10^5
4-Anisate	184	5.23×10^4

[a] all the above experiments were done at pH 5 where the substrates are all ionized.

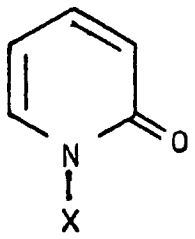
Figure 8. Variation of k_2^* as a function of $[CD]_{corr}$ for phenoxy acetic acid.[a]



[a] values of k_2^* and $[CD]_{corr}$ are calculated from the values of k_2^{app} and $[CD]_t$ given in table A-II using equations 4 and 5 respectively.

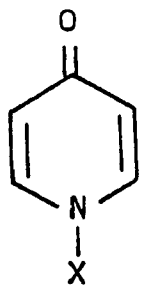
c: PYRIDONES

The rates of bromination of 2- and 4- pyridone (3a, 3b) and their N-methyl derivatives (3c, 3d) have been measured in the presence of α-CD at pH 5. Previous work showed that these compounds undergo reaction on their free base forms at this pH.[26] For all the above substrates at a fixed pH, the bromination reaction exhibits second-order kinetics.[26]



3a; x = H

3c; x = CH_3



3b; x = H

3d; x = CH_3

In the presence of a large excess of substrate, first-order rate constants (k_1^{obs}) have been obtained for bromine disappearance, at varying concentration of α-CD. The second-order rate constants were obtained from k_1^{obs}, taking into account the substrate concentration (Table A-III). The present results for the bromination kinetics of compounds (3a-3d) in the absence of α-CD are in good agreement with those of Paventi.[26]

Similar to the phenols and carboxylate anions, in the presence of increasing amounts of α-CD, the apparent second-order rate constants for pyridones and their N-methyl derivatives do not decrease to the extent, expected from calculations based on eq.12. For all these substrates the observed rate constants are much higher than those calculated assuming only reaction of free species (Table A-III).

Analysis of the observed data based on eq.14 gives plots of k_2^* vs [α-CD), which are quite linear ($r \backsim 0.999$) indicating the involvement of α-CD in the bromination process, Figure 9. The third-order rate constants for this catalytic bromination reaction are calculated from the slopes of the above plots. These rate constants and the observed second-order rate constants at zero [CD] are shown in Table VIII. These results will be discussed in detail in the next sections.

Figure 9. Plots of k_2^* vs $[CD]_{corr}$ for 4-pyridone (3c) and N-methyl 4-pyridone (3d) for the data shown in Table VII.

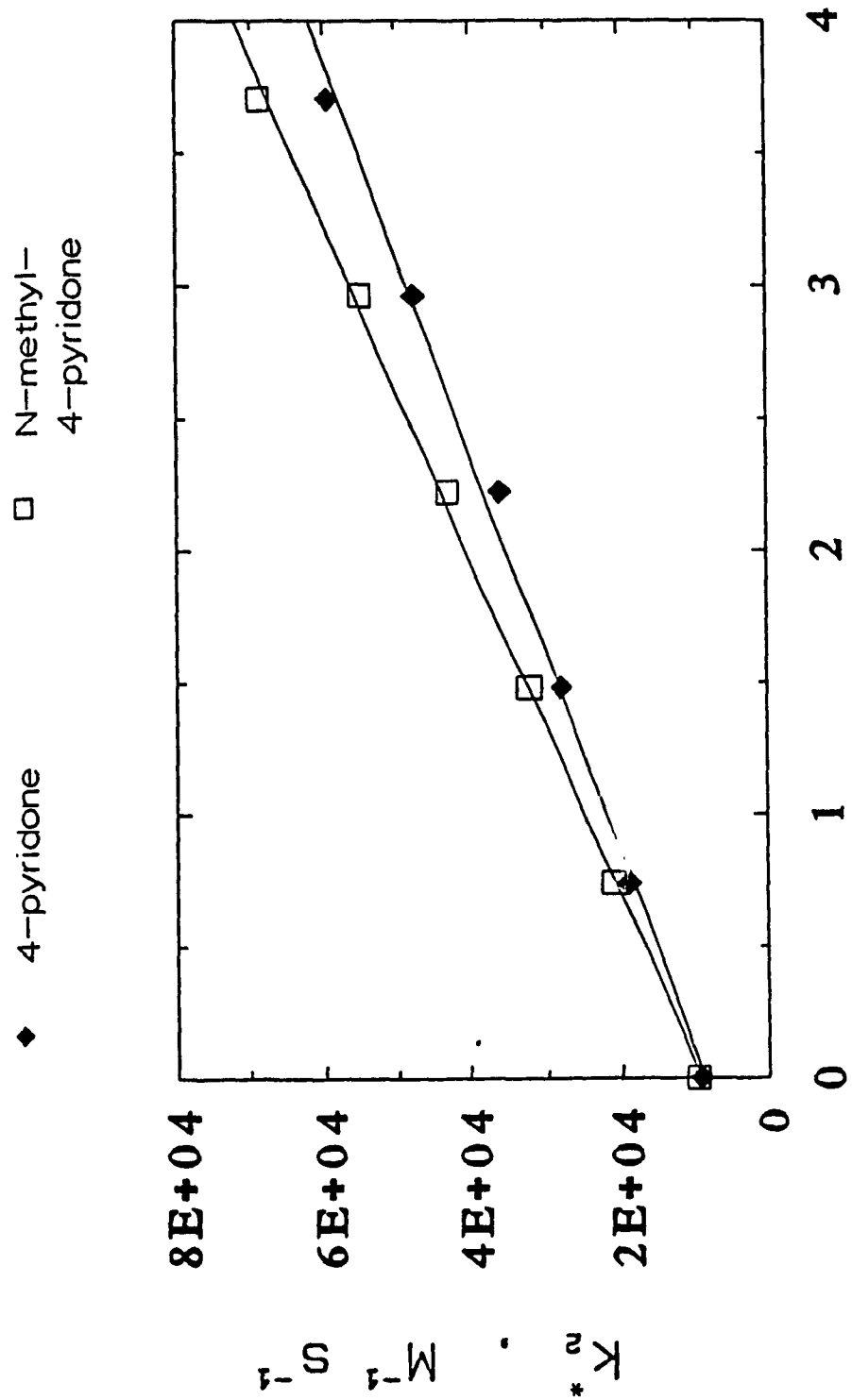


Table VII. The resultant values of k_2^* and $[CD]_{corr}$ for substrates 3c and 3d as treated by eq.14.

$[CD]_t$	$[CD]_{corr}$	$k_2^{app}.10^3$ $M^{-1}s^{-1}$		$k_2^*.10^4$ $M^{-1}s^{-1}$	
mM	mM	3c	3d	3c	3d
0	0	3.27	3.42	0.908	0.951
1	0.741	1.63	1.19	1.91	2.08
2	1.48	1.29	0.76	2.82	3.20
3	2.22	1.08	0.558	3.60	4.27
4	2.96	1.04	0.451	4.78	5.45
5	3.71	0.997	0.389	5.95	6.80

Table VIII. Rate constants for the aqueous bromination of pyridones at pH 5.

substrate, pyridone	No.	k_2 $M^{-1}s^{-1}$	k_3 $M^{-2}s^{-1}$	r[a]
2-	3a	1.80×10^4	1.96×10^7	0.997
N-CH_3-2-	3b	3.45×10^4	6.70×10^6	0.996
4-	3c	9.08×10^3	1.33×10^7	0.998
N-CH_3-4-	3d	9.51×10^3	1.56×10^7	0.999

[a] correlation coefficient for k_2^* vs [CD].

CHAPTER 4
DISSOCIATION CONSTANTS OF CD-SUBSTRATE COMPLEXES

Treatment of the rate data for the substrates in the previous section requires values of K_s for their complexes with α-CD. In some cases these were available from literature, but others had to be determined. In order to determine values of K_s, the competitive inhibition[5] by the substrate of the cleavage of m-nitrophenyl acetate by α-CD was examined. This was done by measuring the rate of m-nitrophenyl acetate cleavage in the presence of a fixed amount of α-CD and varying concentrations of the added inhibitor. As anticipated, the rate effects of α-CD were decreased upon addition of the substrate to the reaction mixture. By determining the extent of inhibition as a function of added inhibitor concentration it was possible to obtain an inhibition constant, K_i which is also the dissociation constant (K_s) of the α-CD-inhibitor complex.

The K_s values of the compounds involved in this study are summarized in Table IX. For the following reaction:

$$E \xrightarrow{k_u} P$$

$$CD + E \underset{K_d}{\rightleftharpoons} CD.E \xrightarrow{k_c} P$$

$$CD + I \underset{K_s}{\rightleftharpoons} CD \cdot I$$

Scheme 3

K_s is the dissociation constant of the 1:1 CD inhibitor complex CD.I, k_u is the uncatalyzed rate constant of the ester E, K_d is the dissociation constant of the 1:1 CD-ester complex CD.E and k_c is the catalyzed reaction constant of the complexed substrate. (Both K_d and k_c were determined by independent kinetic methods)[24,25].

An example of the determination of the dissociation constant of CD-inhibitor is shown in Figure 10, based on the following equation:

$$[I_o] = (k_c - k^{obs}) / (k^{obs} - k_u) [CD]_o K_s/K_d - K_s \text{----- (15)}$$

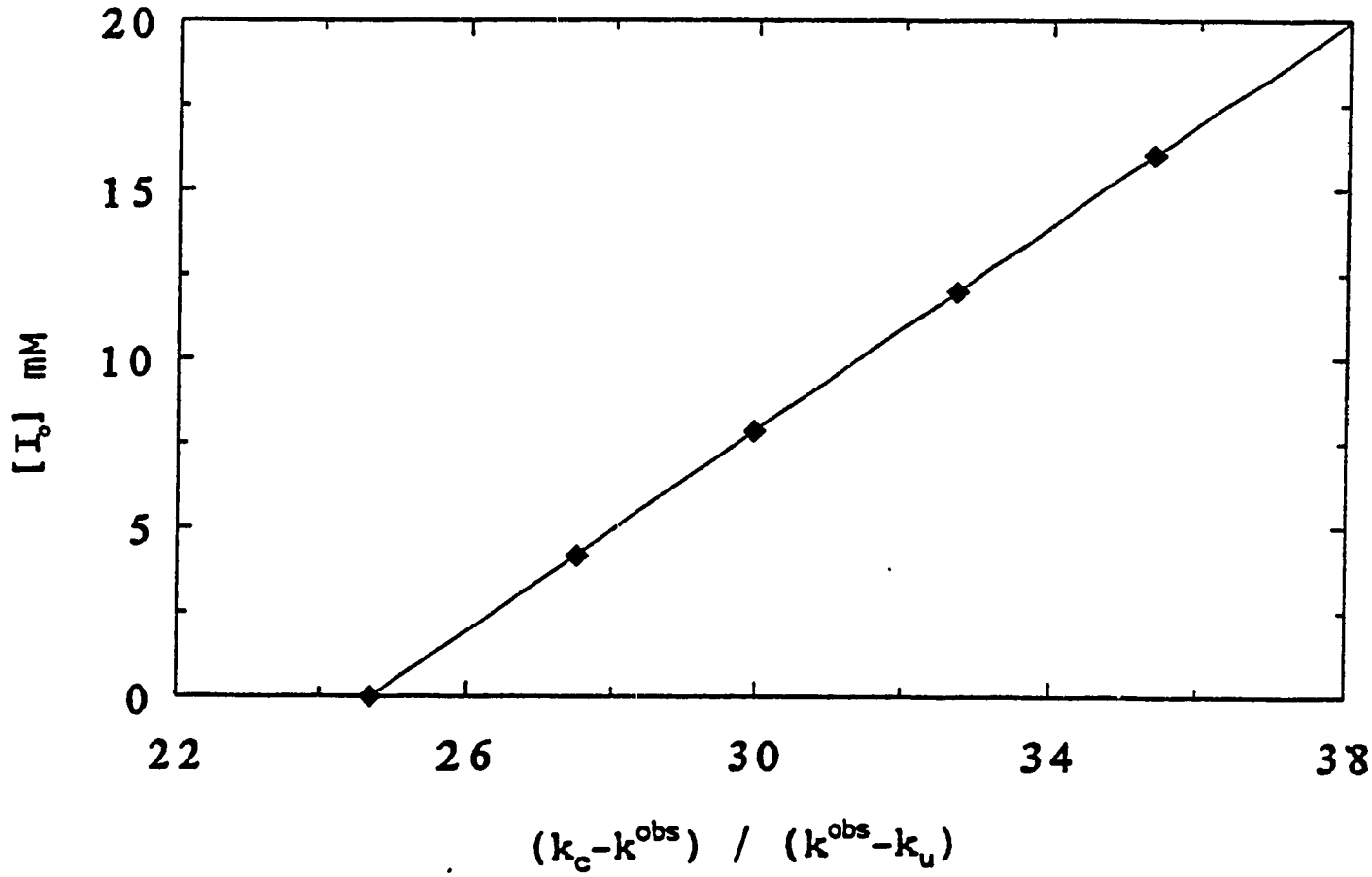
assuming $[CD]_o \gg [E]$ and $[I]_o \gg [CD]_o$ where $[I]_o$ is the concentration of the added inhibitor.

Equation 15 is based on the following approach.[5,7] In the absence of an inhibitor, k^{obs} for ester cleavage is given by [7]

$$k^{obs} = (k_u K_d + k_c [CD]) / (K_d + [CD]) \quad \text{------ (16)}$$

which describes saturation kinetics.

Figure 10. Added inhibitor concentration $[I_o]$, plotted according to eq. (15) as a function of $(k_c - k^{obs}) / (k^{obs} - k_u)$ for the inhibition of cleavage of m-nitrophenyl acetate by 5-sulfosalicylic acid (raw data shown in Table A-IV).



A straight line is obtained (r=0.9998) with the intercept, K_s = 37.2 mM.

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

$$(k^{obs} - k_u) K_d = (k_c - k^{obs}) [CD]$$

$$\text{Therefore } K_d/[CD] = (k_c - k^{obs}) / (k^{obs} - k_u) \text{ ------ (17)}$$

In the presence of an inhibitor I, and provided $[I]_o \gg [CD]_o$, then free CD is given by

$$[CD] = [CD]_o K_s / (K_s + [I]_o)$$

Substitution into eq.(17) gives

$$K_d (K_s + [I]_o) / [CD]_o K_s = (k_c - k^{obs}) / k^{obs} - k_u$$

Cross-multiplication gives

$$K_s + [I]_o = (k_c - k^{obs}) [CD]_o K_s / (k^{obs} - k_u) K_d$$

From which eq. 15 follows. Thus, for the catalysis of the inhibition data we plot $[I]_o$ vs $(k_c - k^{obs}) / (k^{obs} - k_u)$ and from the intercept obtain an estimate of K_s.[5]

In some cases, the inhibition method of determining K_s was not successful. For such cases we tried to extract K_s from the bromination rate data. This approach was used earlier in one or two cases by Bennett.[10] Here a manipulation of the rate expression was used to give a calculated result for K_s by using an Eadie-Hofstee type of analysis[1] as given below. From eq. 13 we define.

$$k_2^* = k_2^{app} / f_B = (k_2 + k_3[CD]) f_s$$

Substitution for f_s from eq.9 and rearrangement lead to

$$k_2^* = k_3K_s + K_s(k_2 - k_2^*) / [CD] \quad \text{------ (18)}$$

Thus, K_s was obtained as the slope of k_2^* vs $(k_2 - k_2^*) / [CD]$, where $k_2 = k_2^{app}/f_B$ measured at zero [CD].

Table IX. Inclusion complex dissociation constants (K_s) for the substrates.

Substrate	No	K_s mM	Reference
Phenol			
4-F	1a	123	28
4-Cl	1b	3.55	28
4-Br	1c	1.4(1.3)	10(28)
4-I	1d	0.468	28
Salicylate			
5-Br	1e	4.74	a
5-SO_3^-	1f	37.2	a
5-NO_2	1g	4.69	b
Carboxylate			
2-Furoate	2a	57.4	a
3-Furoate	2b	73.5	a
2-Thiophene	2c	62.4	a
Phenoxy acetate	2d	56.5	a
2-Phenoxy propionate	2e	64.9	a
2-Anisate	2f	109	a
4-Anisate	2g	31.9	a
Pyridone			
2-	3a	10	b
N-CH_3-2-	3b	2.0	b
4-	3c	9.82	b
N-CH_3-4-	3d	1.22	b

[a] The values of K_s determined by competitive inhibition of the hydrolysis of MNPA.

[b] Fitted value from bromination data.

CHAPTER 5
FORMIC ACID

5.1 INTRODUCTION

Formic acid (HCOOH) is oxidized by bromine in aqueous solution, and the acidity dependence of the rate suggests that reaction occurs on its anion, eq.19[29]. It has recently been reported that in the presence of α-CD, the rate of oxidation of formic acid is slightly increased.[30]

$$HCO_2^- + Br_2 \longrightarrow H^+ + 2Br^- + CO_2 \qquad \text{------ (19)}$$

In the course of present studies the oxidation of HCOOH has also been studied both in the presence and absence of α-CD. We have made similar observations with respect to the effect of α-CD on the rate of the above reaction, but our interpretation of the rate increase differs from that of Han et al.[30]

In earlier work done in this laboratory it was found that the addition of α-CD to Br_2 in 0.01M KBr solution causes large increases in the UV aborbances[12] due to Br_3^-, consiStent with the formation of a strong CD.Br_3^- complex (K_d = 0.17 mM). Also the potentiometric measurements[37] support a dissociation constant of about 0.2 mM for the CD.Br_3 complex. The present work in which the rate constant varies with [Br^-] is thus consistent with dominance of the formation of a CD.Br_3^- complex

in determining the fraction of free Br_2 and the $CD.Br_2$ complex, under the reaction conditions.

In their study, Han's group used potentiometry to measure a CD complexation having K_f = 4690 M^{-1} (K_d = 0.213 mM) under the conditions where Br_3^- formation is significant. ([Br] = 0.1M); it was considered to be due to the formation of a $CD.Br_2$ complex, but no account was taken of the binding of Br_3 to CD. Based on the above study it was concluded that $CD.Br_2$ is half as reactive as Br_2 towards formate ion and that rate increases arise because CD converts unreactive Br_3 to reactive $CD.Br_2$.[30] In contrast, the previous studies[10] and the present work on the effects of CD on brominations have used K_d = 2.1 mM for $CD.Br_2$, as reported by Breslow and Campbell.[11] Analysis of the rate increases with [CD] suggests that $CD.Br_2$ is more reactive ($\backsim$10x) than free Br_2 towards formate ion, as was found for phenols.[10]

In addition to the significant catalysis observed in the presence of α-CD, the present work also reports a dependence of the above oxidation reaction on pH, consistent with the earlier studies.[29]

5.2 RESULTS

The oxidation of HCO_2H by Br_2 has been carried out using a large excess of HCO_2H and Br (0.1M) at pHs 2.08 and 5, both in the presence of and absence of α-CD. Pseudo-first-order rate constants were obtained by monitoring the bromine

disappearance by stopped flow techniques.[15,16]

The first-order rate constant was found to be a direct function of the substrate concentration [S]. Figure 11 shows this dependence, corresponding to the results in Table X. Clearly, in the presence of α-CD, as in its absence, the reaction follows overall second-order kinetics, first order in HCO_2H or HCO_2^- and first order in Br_2. The pseudo first-order rate constants for formic acid at two pHs are given in Table A-VI. The second-order rate constants can be derived from k_1^{obs} by taking into account the [S].

In the presence of an excess of Br^-, the observed second-order rate constant k_2^{obs} for the uncatalyzed reaction is represented as:

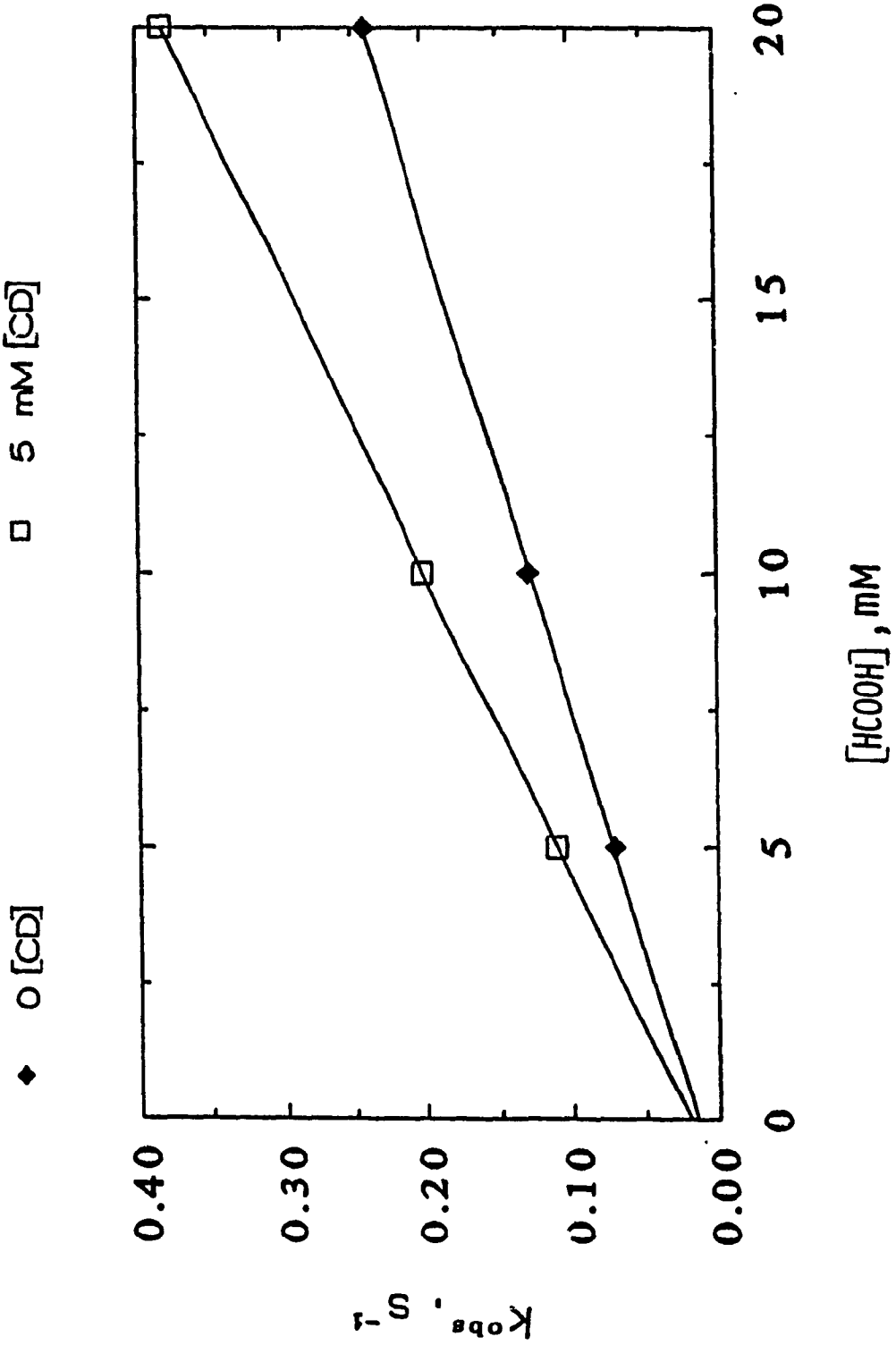
$$k_2^{obs} = k_2^{app} / f_B$$

Where f_B is the fraction of free bromine corrected by taking into account the Br_3^- formation (eq.2).

Table X. Pseudo first-order rate constants for the oxidation of formic acid as a function of substrate concentration at pH 5.

	At 0 CD	At 5mM CD
$[HCO_2H]$ mM	k_1^{obs} s^{-1}	k_1^{obs} s^{-1}
5	0.071	0.111
10	0.130	0.201
20	0.241	0.382

Figure 11. Variation of the first-order rate constant $k_1^{obs}(s^{-1})$ as a function of substrate concentration [S] for formic acid.



It has been observed that in the presence of increasing amounts of α-CD, the rate constant for the oxidation of formic acid at any given pH increases by a factor of 1.4. (Table XI). Considering the complexations of Br_2 and Br_3 with α-CD, the rate should have been strongly inhibited if the only reaction occurring was between the free substrate and free bromine. It is therefore suggested that there is a second oxidation pathway in the presence of α-CD, which overcomes any suppression of the normal oxidation of formate with bromine:

$$HCO_2^- + Br_2 + CD \xrightarrow{k_3} P$$

If such a process is involved, k_2^{app} has contributions from the normal bromination and this additional process. Ignoring the very weak binding of formic acid with CD (K_d = 250 mM)[30] eq. 14 then becomes.

$$k_2^* = k_2^{app} / f_B = k_2 + k_3 [CD] \qquad \text{------ (20)}$$

Figures 12a and 12b show the results obtained at two different pHs for the aqueous bromination of formic acid, treated according to the above equation (Table XII). These plots are quite linear (= 0.9997 and 0.9989) giving the third-order rate constants $k_3(M^{-2}s^{-1})$ to be 5.08×10^3 and 1.75×10^5 at pH 2.08 and pH 5 respectively. For HCO_2^- at pH 5, both the catalyzed and uncatalyzed rate constants are higher than those at pH 2

Table XI. The apparent second-order rate constants for the oxidation of formic acid.[a]

[CD] mM	k_2^{app} $M^{-1}s^{-1}$ pH 2.08	pH 5
0	0.339	11.4
1	0.429	15.7
2	0.428	16.0
3	0.430	15.4
4	0.466	15.7
5	0.451	15.8

[a] [S] = 0.1M, $[Br_2]$ = $5x10^{-5}$ M, $[Br^-]$ = 0.1M.

indicating the reaction involves the anion of the acid.[29]

The effect of varying [Br] on the rate of the above reaction in the presence and absence of α-CD has also been measured (Table XIII). In the absence of α-CD, the apparent second-order rate constant is given by:

$$k_2^{app} = k_2 f_B \qquad (= 10)$$

where f_B is the fraction of free bromine (eq.3) and is expressed as:

$$f_B = K / (K + [Br^-]) \quad (=3)$$

so that $k_2^{app} = k_2 K / (K + [Br^-])$

where k_2 is the observed second-order rate constant and K, the dissociation constant of Br_3^- is 0.0562M. The above equation requires a reciprocal relationship between k_2^{app} and $[Br^-]$:

$$1 / k_2^{app} = 1 / k_2 + [Br^-] / k_2 K \qquad \text{------ (21)}$$

Figure 13a shows a plot where $1/k_2^{app}$ varies linearly with $[Br^-]$ for the reactions, in the absence of α-CD.

Figure 12. Plots of k_2^* vs $[CD]_{corr}$ for formic acid for the data shown in Table XII at pH 2.08 (a) and at pH 5 (b), based on eq.20.

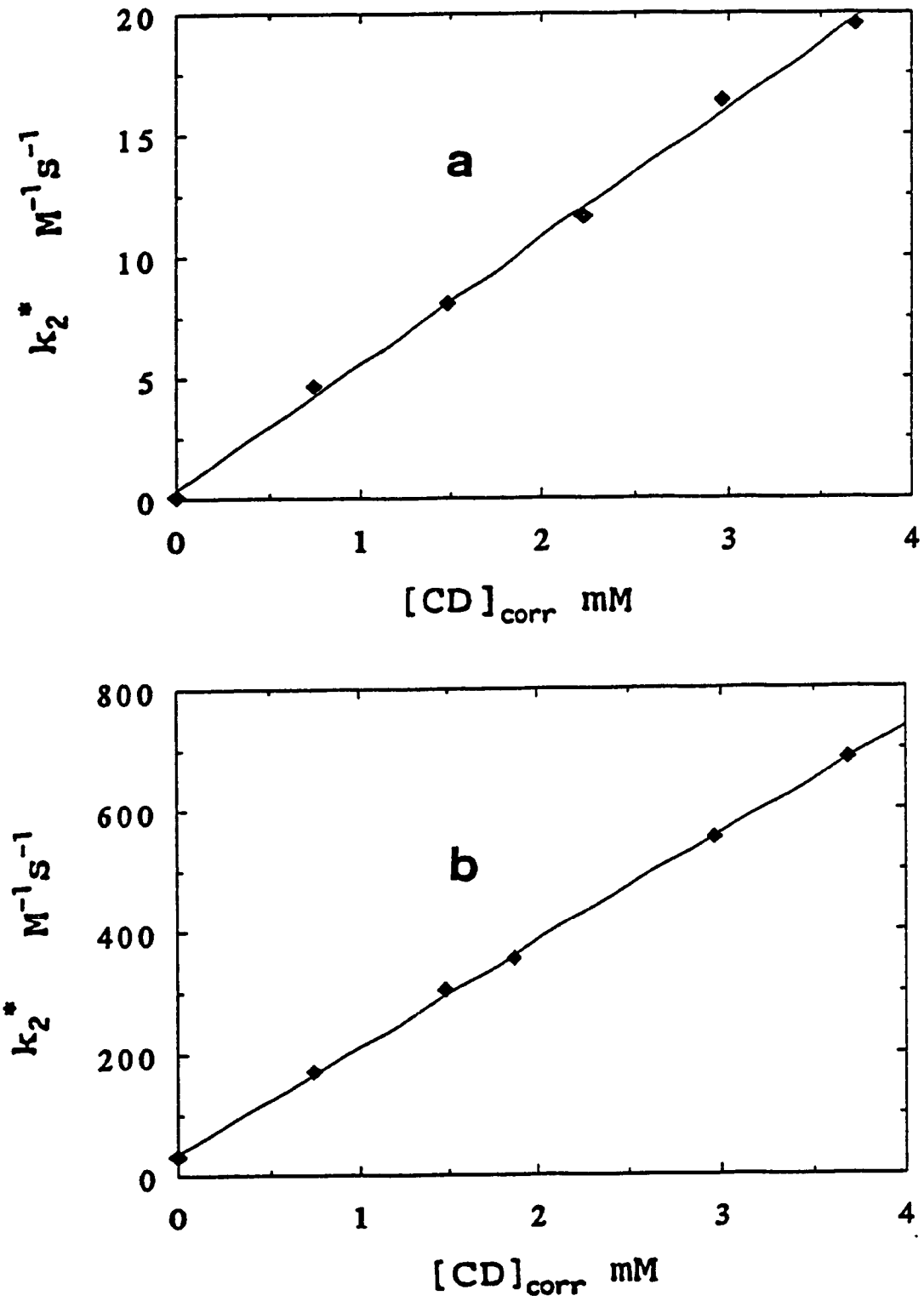


Table XII. (a) Rate constants for the oxidation of formic acid at pH 2.08.

$[CD]_t$ mM	$[CD]_{corr}$ mM	k_2^{app} $M^{-1}s^{-1}$	k_2^* $M^{-1}s^{-1}$
0	0	0.339	0.942
1	0.741	0.429	4.67
2	1.48	0.428	8.13
3	2.22	0.430	11.7
4	2.96	0.466	16.4
5	3.71	0.451	19.5

(b) Rate constants for the oxidation of formic acid at pH 5.

$[CD]_t$ mM	$[CD]_{corr}$ mM	k_2^{app} $M^{-1}s^{-1}$	k_2^* $M^{-1}s^{-1}$
0	0	11.4	31.7
1	0.741	15.7	1.71×10^2
2	1.48	16.0	3.01×10^2
2.5	1.85	15.4	3.55×10^2
4	2.96	15.7	5.53×10^2
5	3.71	15.8	6.84×10^2

With α-CD present more complex behaviour is anticipated because of the binding of the substrate and other species (see Chapter 5, Section 5.1). However, the binding of formic acid is very weak and can be ignored.[30] Therefore eq.10 is still valid but f_B has the complex form given in eq. 8., as a result of which $1/k_2^{app}$ also depends on $[Br^-]$.[12] Such behaviour is seen in Figure 13b, and so both reactions show inverse dependences on $[Br^-]$.

For the reactions in the absence of α-CD the dependence arises due to the increasing formation of unreactive Br_3^- [30]; in the presence of CD it is consistent with dominance of the formation of the $CD.Br_3^-$ complex which is also unreactive.[10,12] Thus in both cases the reaction is slower at higher $[Br^-]$ because $[Br_2]$ and $[CD.Br_2]$ are reduced by the Br_3^- and $CD.Br_3^-$ formation. The detailed interpretation of the results and their comparison with those of earlier studies will be discussed in the next section.

Figure 13. Variation of $1/k_2^{app}$ with [Br^-] at pH 2.08.

(a) [α-CD] = 0;

(b) [α-CD] = 5 mM.

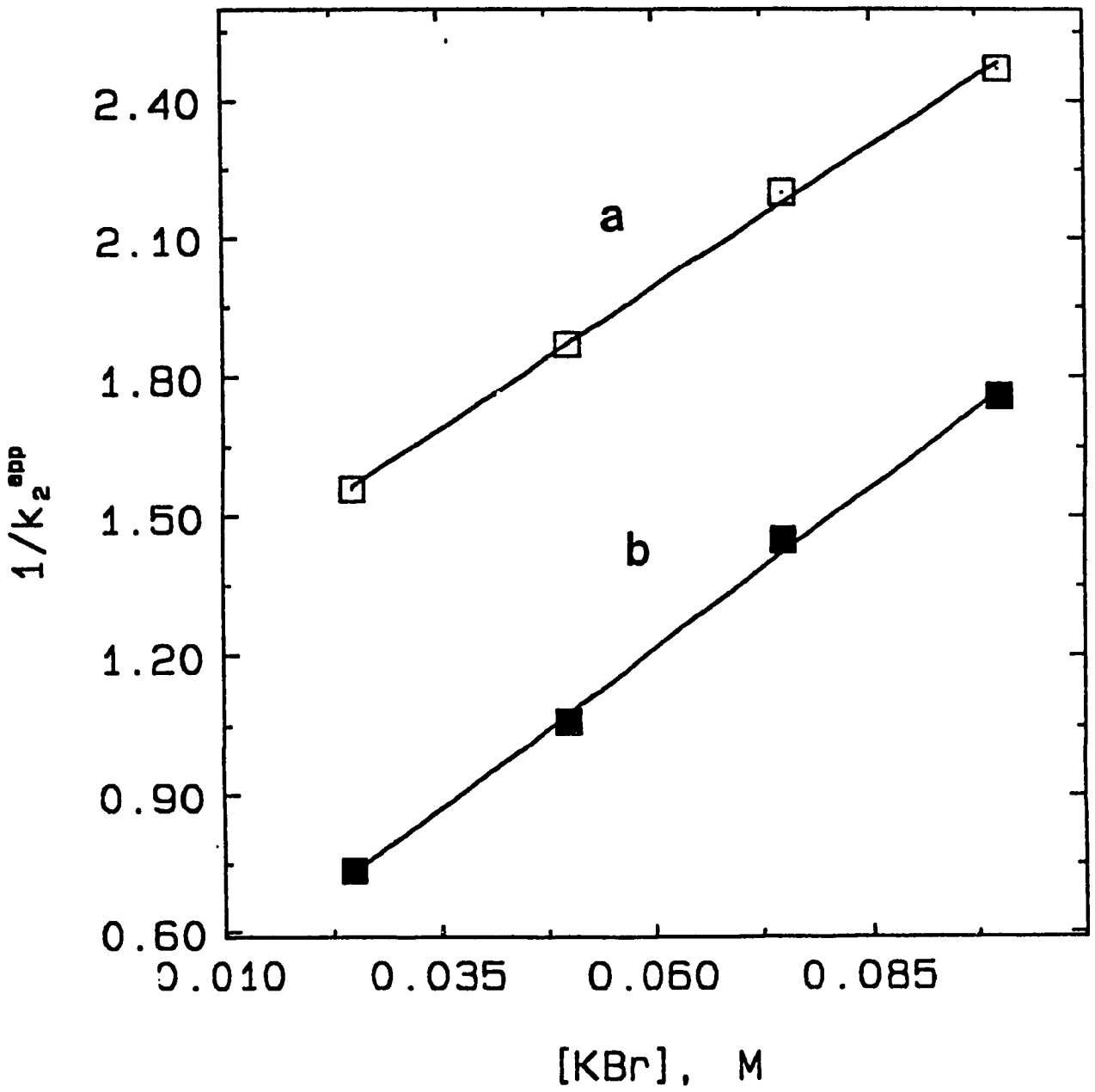


Table XIII. Rate parameters for the plots shown in Figure 13 as treated by eq. 21, at pH 2.08.

KBr	k_2^{app} $M^{-1}s^{-1}$		$1/k_2^{app}$	
M	[CD]=0	[CD]=5mM	[CD]=0	[CD]=5mM
0.025	0.643	1.36	1.555	0.7353
0.05	0.534	0.946	1.873	1.057
0.075	0.454	0.688	2.203	1.453
0.1	0.405	0.569	2.467	1.757

CHAPTER 6

DISCUSSION

As is evident from the results presented above, α-CD exerts significant effects on the rates of bromination of several organic compounds. All of the substrates studied react via a catalytic bromination pathway in the presence of α-CD which partially or totally makes up for the rate retardations due to the complexation of reactants.

The catalytic effect of α-CD may be due to either a covalent interaction or a non-covalent interaction between CD and the substrate. Covalent catalysis involves a distinct covalent interaction between the substrate and the secondary hydroxyl group of the CD molecule. Such interaction is strongly dependent on the position of the substituent on an aryl substrate.[3] No such dependence has been observed in the present or previous study.[10]

The other possibility is the non-covalent catalysis which arises due to the microsolvent effect.[1] This effect is either due to the apolar cavity of CD, a conformational effect as a result of the geometric requirements of inclusion, or a consequence of complexation bringing two reactants together. The occurrence of catalysis simply on the basis of microsolvent effect is not evident since the rate of bromination of phenol and other substrates is much slower in less polar media. (In water the attack of bromine on

phenol:[10] $k_2 = 4.11 \times 10^5\ M^{-1}s^{-1}$, is 68500 times faster than in acetic acid:[34] $k_2 = 6.0\ M^{-1}s^{-1}$)

Nevertheless for the bromination reactions of the substrates studied so far, there exists the following ways which are most probable for the CD catalyzed reaction:

A) $S + Br_2 \,.\, CD \longrightarrow P$

B) $S.\ CD + Br_2 \longrightarrow P$

C) $S.\ CD \,.\, Br_2 \longrightarrow P$

Model 'A' represents the reaction between the free substrate and encapsulated bromine, model 'B' shows the attack of free bromine on the complexed substrate, and model 'C' represents the reaction occurring via the formation of a ternary complex of the substrate, CD and bromine. Before discussing the most likely way of catalysis for the reaction, other possibilities will be considered first.

Earlier studies on anisole[12] and phenols[10] indicated that the rate variation with changing [Br^-] is inconsistent with the involvement of Br_3^- as a catalytic bromination species. Similarly, from the present work on the oxidation of formic acid, Br_3^- and CD.Br_3^- do not have any significant reactivity. Likewise, the studies in which pH was varied failed to indicate any reaction occurring via HOBr or a hypobromite ester of α-CD.[10,12] The bromide dependence of rate constants was also inconsistent with such mechanisms.[12] The formation of such species is highly unfavourable under the present reaction conditions, pH <5, [Br^-] = 0.1M, where less than 1%

of the total bromine exists as HOBr.[12]

Also the catalysis involving the termolecular complex, model "C", is unlikely. The space filling models (CPK) indicate that it is physically impossible to include both the reactants in the cavity of a single CD molecule. However, it is conceivable that one reactant might be in the CD cavity and the other just outside. All that can really be said is that there is no compelling evidence (yet) that requires a ternary complex.

Most likely CD catalyzes the reaction by facilitating the approach of the two reactants. Considering the space restriction factor there seems to be only two possibilities for the bimolecular collision of one reactant with the CD complex of the other i.e model 'A' or model 'B'. These will be discussed now in detail for each series of compounds studied.

6.1 PHENOLS

Model 'A' in the above section can be represented by the pathway shown in eq.22, below.

$$S + CD + Br_2 \underset{K_b}{\rightleftharpoons} S + CD.Br_2 \xrightarrow{k_2^A} P\text{------} \quad (22)$$

Likewise, model 'B' can be represented by the pathway in eq. 23.

$$S + CD + Br_2 \underset{K_S}{\rightleftharpoons} S \,.\, CD + Br_2 \xrightarrow{k_2^B} P \text{ ------ (23)}$$

For the above two models, eq.14 can be represented by two equivalent equations:

$$k_2^* = k_2 + k_2^A[CD]/K_B \text{ ------ (24)}$$

$$k_2^* = k_2 + k_2^B[CD]/K_s \text{ ------ (25)}$$

Where the rate constants k_2^A and k_2^B are for the two catalyzed pathways ('A' and 'B'), and K_B and K_s are the dissociation constants of complexed bromine and complexed substrate. Thus, equating (14) with (24) or (25), $k_3 = k_2^A/K_B$ or k_2^B/K_s respectively. From these equivalences the rate constants for the two reaction models 'A' and 'B' have been evaluated for four p-halo-phenols; these are presented in Table XIV.

It can be observed that the k_2^A and k_2 values for all four phenols show similar trends toward the substituents, as was observed for other substituted phenols. In the earlier studies on phenols, Tee and Bennett found that this similarity results in a strong correlation between the rate constants for the catalyzed (k_3) and the uncatalyzed (k_2) brominations.[10] It can also be seen that the ratio, k_2^A/k_2 (Table XIV), which measures the efficiency of catalysis as a function of substituent change, lies between 4.6 and 7.2, indicating a more or less similar extent of catalysis for all four substrates

substrates.

The behaviour observed for the four p-halo phenols fits in with that observed for other phenols.[10] A plot of log k_2^A vs log k_2 for a series of several mono and disubstituted phenols is quite linear (r = 0.986) with a slope of 1.13 (sd = 0.06). Figure 14. This indicates that the uncatalyzed and catalyzed rate constants are equally sensitive to the nature of the substituent consistent with model 'A'.

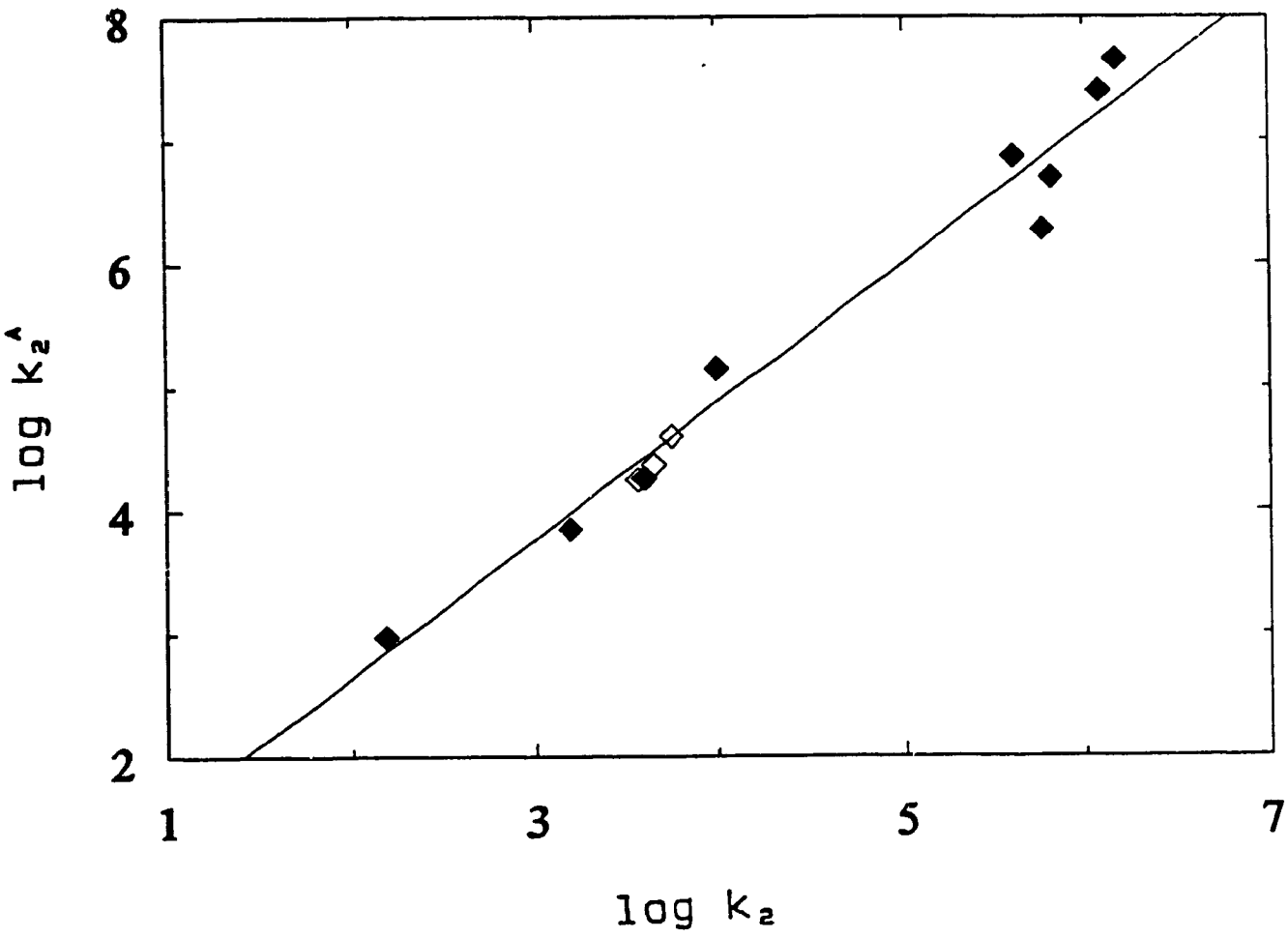
Table XIV. Rate constants evaluated for the reaction models 'A' and 'B ' for phenols.[a]

Phenol	$k_2, M^{-1}s^{-1}$	$k_2^A=k_3\ K_b$	k_2^A/k_2	$k_2^B=k_3K_s$	k_2^B/k_2
4-F	4350	$2.35x10^4$	5.40	$1.38x10^6$	$3.17x10^2$
4-Cl	3600	$1.76x10^4$	4.89	$2.94x10^4$	8.17
4-Br[b]	3900	$1.79x10^4$	4.58	$2.51x10^4$	6.43
4-I	5531	$3.99x10^4$	7.21	$3.47x10^6$	23.1

[a] The behaviour observed for the four p-halo phenols fits in with that observed for other phenols.[10]

[b] For this compound, data is taken from the literature.[10]

Figure 14. A plot of log k_2^A vs log k_2 values for phenols.

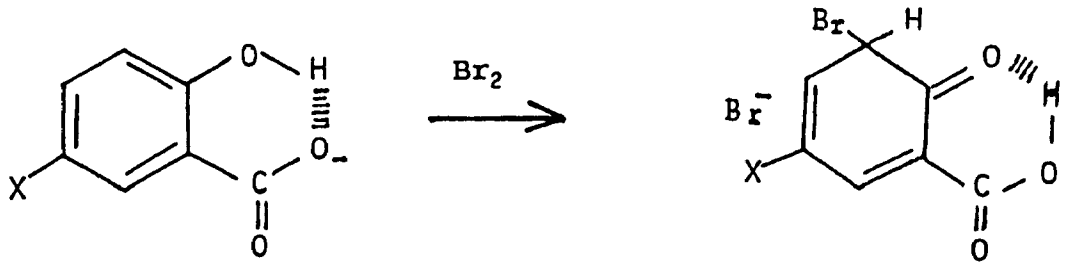


■ ref 10 □ This work (Table XIV)

6.2 SALICYLATE ANIONS

Earlier studies[23] and the present work on the uncatalyzed bromination of salicylate anions (Table III) have shown that these anions, which are o-hydroxy benzoates, are more reactive than the corresponding phenols. Also in their work, Tee and Iyengar found that the substituents' effects on these compounds are less significant than those on the phenols. The Hammet plot for 5-substituted salicylate ions gives $\rho^+ = -2.94$ and for the same type of plot for p-substitued phenols, the ρ^+ value obtained is -5.21.

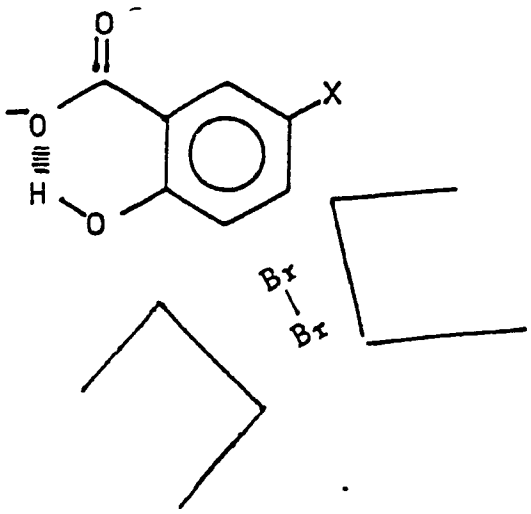
These differences in reactivity and selectivity (the ρ values) were attributed to the following reaction of salicylates where the attack of bromine occurs on the intramolecular hydrogen-bonded salicylate anion (Scheme 4). Due to assistance from internal proton transfer, the effect of 5-substituents should be less than that in p-substituted phenols.[23]



o-bromo-product

Scheme 4

However, in the presence of α-CD, it has been observed that these compounds behave in a manner similar to phenols, even though salicylate anions are more reactive. For example, there is a strong correlation between k_2 and k_3 values (Table III). This indicates the common effect of α-CD on the bromination reactions of phenols and salicylates; it is consistent with the effect of α-CD mainly on increasing the reactivity of Br_2 by complexation (Scheme 5).



Scheme 5

6.3 INTERPRETATION OF RESULTS IN TERMS OF K_{TS} VALUES "PHENOLS AND SALICYLATE IONS"

The most important factor in catalysis is the stabilization of the reaction transition state by the catalyst. The pseudo dissociation constants, K_{TS} have been found to be very useful in estimating the strength of binding of transition states, in reactions mediated by cyclodextrins.

Reactions which require two substrate molecules in order to reach the transition state may be treated as follows:

$$S_1 + S_2 \xrightarrow{k_2} P$$

$$k_2 = Q\ [TS]\ /\ [S_1][S_2],\ \text{where}\ Q = k_B T\ /\ h$$

This equation follows from transition state theory. Similarly, with CD present:

$$S_1 + S_2 + CD \xrightarrow{k_3} P$$

$$k_3 = Q\ [TS.CD]\ /\ [S_1]\ [S_2]\ [CD]$$

From these two constants we define

$$K_{TS} = [TS]\ [CD]\ /\ [TS\ .\ CD]\ = k_2\ /\ k_3 \quad \text{------(26)}^{36}$$

The constant K_{TS} is the pseudo dissociation constant of the transition state of the catalyzed reaction (TS.CD) into the transition state of the normal reaction (TS) and the catalyst CD. Values of K_{TS} are obtained directly from the rate data without any assumptions being made about the mechanisms of the mediated and normal reactions. Therefore, the sensitivity or

insensitivity of the value of K_{TS} (and log K_{TS}) to the changes in substrate structure can allow a distinction to be made between different modes of binding of the transition state, and a comparison to initial state binding.[36]

Using this approach, further evidence of the catalysis occurring via pathway 'A' for the reactions of both phenols and salicylates can be obtained. Values of K_{TS}, calculated from the ratio of the rate constants for the uncatalyzed and catalyzed reactions (k_2 and k_3), are shown in Table XV. For these compounds, values of K_{TS} vary only from 0.21 to 0.67 mM. Also they fall in the same range (0.07 to 0.8 mM) obtained[36] previously for phenols and phenoxides.

As seen in Table XV, the above values of K_{TS} do not correlate with the K_s values of the substrates. This insensitivity of K_{TS} to the nature and position of the substitutents strongly favours the transition state in which the aromatic substrate stays outside the cavity of the CD during the bromination process. Likewise, the similarity of K_{TS} values for a wide range of substrates is consistent with bromine being in the α-CD cavity in the transition state.

Table XV. Constants for the CD-mediated bromination of phenols and salicylate anions.

Substrate	k_2 $M^{-1}s^{-1}$	k_3 $M^{-2}s^{-1}$	K_s mM	K_{TS} mM
Phenol				
4-F	4350	1.12×10^7	123	0.39
4-Cl	3600	8.4×10^6	3.55	0.43
4-Br[a]	3900	8.5×10^6	1.4	0.46
4-I	5531	1.90×10^7	0.468	0.29
Salicylate				
5-Br	1.50×10^5	7.28×10^8	4.74	0.21
5-SO_3^-	1.10×10^5	1.83×10^8	37.2	0.601
5-NO_2	1.61×10^4	2.40×10^7	4.69	0.67

[a] For this compound the data are taken from the literature.[10]

6.4 CARBOXYLATES

The results obtained for the uncatalyzed bromination of the carboxylates 2a-2g, show varying degrees of reactivity towards the normal electrophilic substitution: the 3-furoate ion is the most reactive (k_2 = 5.23x10^4 $M^{-1}s^{-1}$); the 4-anisate ion is the least reactive, with k_2 = 184 $M^{-1}s^{-1}$. (Table VI).

From the values of observed and calculated rate constants (for example for 2-furoate, Table IV),it is clear that there is some catalytic process in the bromination of above substrates in the presence of α-CD. Therefore, the corresponding third-order rate constants (k_3, Table VI) have been analyzed in terms of two reaction models, as shown in Table XVI.

As it can be seen from the values of k_2^A, the analysis based on model 'A' does not correspond to efficient catalysis. Most of the values show rate retardations ($k_2^A/k_2<1$), in place of rate increases. Analysis of the same data on the basis of model 'B' however, gives a reasonable amount of catalysis, as was expected. In the presence of α-CD, the difference between the maximum and minimum rate constants is of the order of 1730; larger than the one for the uncatalyzed bromination, 284X. This may indicate that the bromination of compounds 2a-2g, in the presence of α-CD is slightly more sensitive to the structure of the substrate (i.e. to the substituent effects). In other words, it could be the CD-substrate binding which causes the rate changes.

Table XVI. Rate constants evaluated for carboxylate ions for two reaction models[a].

Substrate	No	$k_2^A=k_3K_B$	k_2^A/k_2	$k_2^B=k_3K_s$	k_2^B/k_2
2-furoate	2a	2.07×10^4	0.892	5.61×10^5	24.2
3-furoate	2b	8.32×10^4	1.59	2.89×10^6	55.3
2-thiophene carboxylate	2c	5.99×10^2	0.445	1.77×10^4	13.2
phenoxy acetate	2d	7.96×10^3	0.510	2.16×10^5	13.8
2-phenoxy propionate	2e	1.13×10^4	0.383	3.50×10^5	11.9
2-anisate	2f	1.88×10^3	0.096	9.76×10^5	49.8
4-anisate	2g	2.0×10^2	1.09	1.67×10^3	9.08

a: Evaluated from the values of k_3 given in Table V1. Units of k_2^A and k_2^B are $M^{-1}s^{-1}$.

If that is so, one may also expect some kind of relationship between the binding modes of the substrates and those of the transition states with CD,[36] for the above compounds. No such correlation has been found; a plot of log K_s vs log K_{TS}, (Table XVII) gives nonsensical results and very poor linearity (r=0.146).

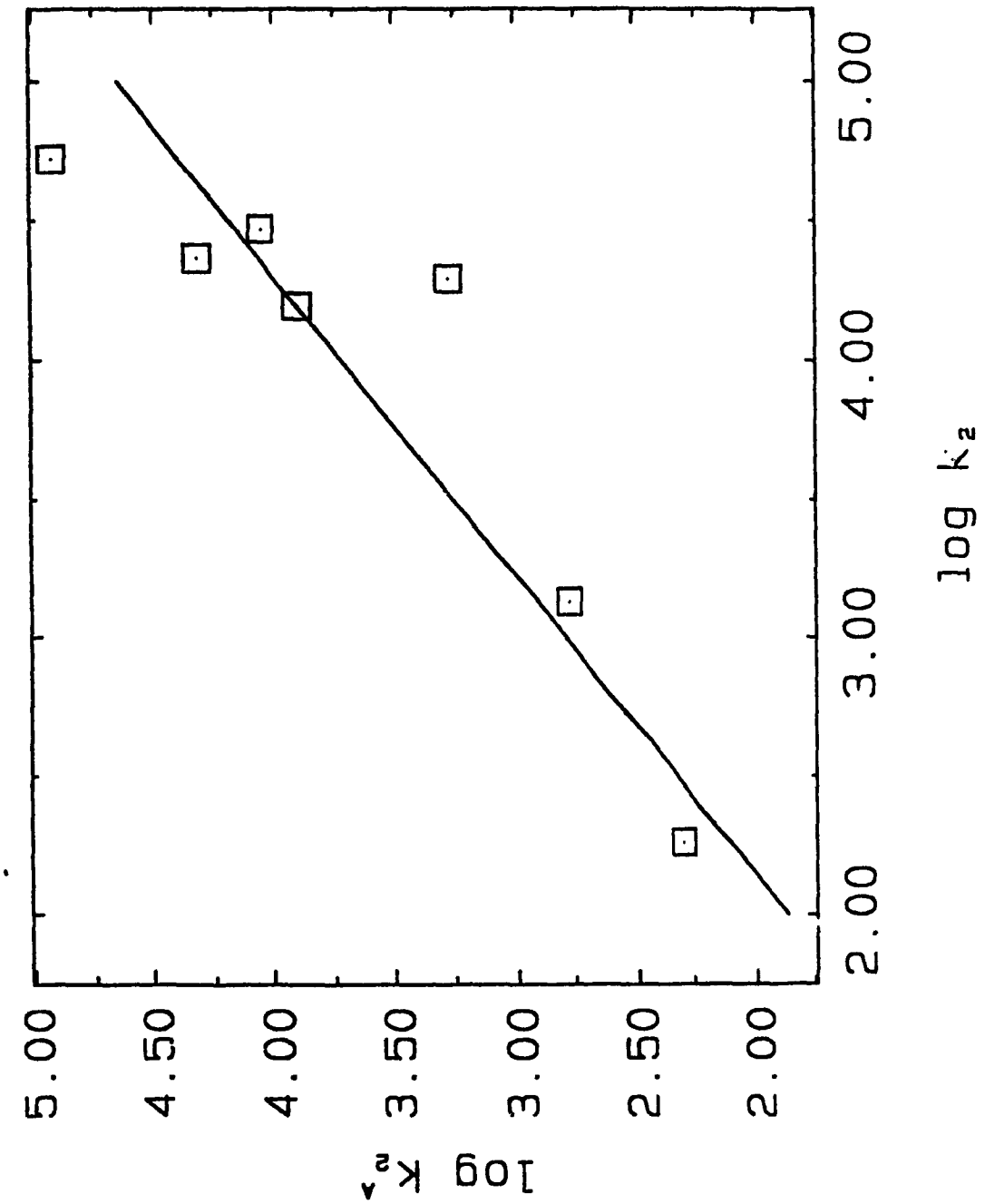
Considering then the model 'A' only, values of log k_2^A are plotted against those of log k_2, Figure 15. From the slope of this plot (0.929), it may be suggested that the catalyzed and the uncatalyzed rate constants (k_2^A and k_2) respond almost equally to the structure of the substrate. This insensitivity to the substituent effects is consistent with the bromination pathway which involves the attack of complexed bromine on the free substrate. However, the reasons for inefficient catalysis for these compounds are ambiguous. Similar rate changes were found previously for anisole and p-methyl anisole; where free bromine is about twice as reactive as the bromine-CD toward the free substrate.[12]

As is clear from the above discussion, carboxylate anions behave differently from phenols and salicylate anions in the CD-mediated bromination reactions. Although the present data fully justifies this behaviour, their interpretation is inconsistent with that found for other substrates in the present study. This discrepancy may be related to some unknown process going on during the catalytic bromination of these compounds that is not taken care of in analyzing the data.

Table XVII. Constants for the CD-mediated bromination of carboxylate ions.

Substrate	k_2 $M^{-1}s^{-1}$	k_3 $M^{-1}s^{-1}$	K_s mM	K_{TS} mM
2-furoate	2.32×10^4	9.85×10^6	57.4	2.36
3-furoate	5.23×10^4	3.96×10^7	73.5	1.32
2-thiophene carboxylate	1345	2.85×10^5	62.4	4.72
phenoxy acetate	1.56×10^4	3.79×10^6	56.5	4.12
2-phenoxy propionate	2.95×10^4	5.39×10^6	64.9	5.47
2-anisate	1.96×10^4	8.95×10^5	109	6.10
4-anisate	184	5.23×10^4	31.9	3.52

Figure 15. A plot of log k_2^A vs log k_2 values for carboxylate ions, 2a-2g.



6.5 PYRIDONES

Similar to other organic substrates, the enhanced reactivity of pyridones and their N-methyl derivatives is attributed to an additional bromination process which accounts for the catalysis by α-CD.

A significant difference between the calculated and the observed apparent second-order rate constants (Table A-III) clearly indicates the importance of CD-encapsulation of bromine or that of the substrate in the catalytic process. Therefore, the rate constants have been evaluated for two reaction models 'A' and 'B' (Table XVIII) so as to investigate which one of these is involved in catalysis.

As can be seen from Table XVIII, the results are more consistent with pathway 'A'. The almost similar amount of catalysis (k_2^A/k_2) observed for these compounds agrees quite well with the reaction of complexed bromine on the free substrate. Analysis based on model 'B' gives significant rate increases for the above compounds. Though this favours the bromination pathway involving the complexation of the substrate, no evidence is found on the basis of binding constants of the substrates (K_s) or of the transition states (K_{TS}), Table XIX. The K_{TS} values show no correlation with the structure of the substrates contradicting the above results for catalysis via pathway 'B'.

Table XVIII. Rate constants evaluated for two reaction models for pyridones.[a]

Substrate Pyridone	No	$k_2^A=k_3K_B$	k_2^A/k_2	$k_2^B=k_3K_s$	k_2^B/k_2
2-	3a	4.12×10^4	2.29	1.96×10^5	10.9
N-CH_3-2-	3b	5.65×10^4	1.64	5.38×10^4	1.56
4-	3c	2.79×10^4	3.07	1.31×10^5	14.4
N-CH_3-4-	3d	3.28×10^3	3.34	1.90×10^4	2.0

[a] Evaluated from the values of k_3 given in Table VIII. Units of k_2^A and k_2^B are $M^{-1}s^{-1}$.

In contrast, the insensitivity of K_{TS} values to the nature and position of the substituents for compounds 3a-3d favours a transition state in which the substrate stays outside the CD cavity, that is, model 'A'. This is consistent with the effect of α-CD being mostly on increasing the reactivity of bromine by complexation.

Table XIX. Constants for the catalytic bromination of pyridones.

Substrate, Pyridone	k_2 $M^{-1}s^{-1}$	k_3 $M^{-1}s^{-1}$	K_s mM	K_{TS} mM
2-	1.80×10^4	1.96×10^7	10.0	0.92
N-CH_3-2-	3.45×10^4	2.69×10^7	2.0	1.3
4-	9.08×10^3	1.33×10^7	9.8	0.68
N-CH_3-4-	9.51×10^3	1.56×10^7	1.2	0.61

6.6 FORMIC ACID

The present results for the oxidation of formic acid in the presence of α-CD are consistent with a catalytic bromination process, as was observed by Han et al.[30]

Under the present reaction conditions, the disappearance of Br_2 is first order:[29,30]

$$Br_2 \xrightarrow{k_1} \text{Products} \qquad \text{------ (27)}$$

In the presence of CD there is an additional process, which is attributed to the reaction of formate ion with the CD.Br_2 complex.[30]

$$CD + Br_2 \underset{K_B}{\rightleftharpoons} CD \cdot Br_2 \xrightarrow{k_2} \text{Products------ (28)}$$

Since formic acid binds very weakly with α-CD[30], this binding can be ignored. Then, the observed first-order rate constant should have the form:

$$k^{obs} = (k_1 + k_2[CD]/K_B)\ f_B \qquad \text{------ (29)}$$

where f_B is the fraction of free bromine. The difference between the present approach and that of Han et al[30] is in respect of the form chosen for f_B. The present approach uses f_B as follows:

$$f_B = KK_BK_T/K_BK_T(K + [Br^-]) + [CD](KK_T+K_B[Br^-]) \qquad (=eq.8)$$

where K, K_B, and K_T are the dissociation constants of Br_3^-, $CD.Br_2$, and the $CD.Br_3^-$ complex, respectively with K=0.0562M, K_B=2.1 mM and K_T=0.17 mM.[10,12]

If the binding of Br_3^- to CD is very weak and negligible, K_T is large and the above equation becomes:

$$f_B = KK_B/(K_B(K + [Br^-]) + [CD]K) \qquad \text{------ (30)}$$

This is essentially the form used by Han and coworkers, with K=0.0588 M and K_B=0.213 mM.[30]

In eq.8, the dominant terms in the denominator involve $[Br^-]$, so that f_B decreases from 0.059 to 0.017 for $[Br^-]$=0.025 - 0.100M([CD]=5 mM). Adding bromide ion produces more Br_3^- and hence $CD.Br_3^-$, at the expense of Br_2 and $CD.Br_2$. In contrast, in eq.30 the dominant term is [CD]K so that f_B hardly varies (0.040-0.038) under the same conditions. Increasing $[Br^-]$ produces more Br_3^-, but the fraction of $CD.Br_2$ is large and almost constant (0.94-0.90).

The present kinetic results for the variation of the apparent rate constant with $[Br^-]$ are consistent with the dominance of the formation of the unreactive $CD.Br_3^-$ complex. Independent potentiometric studies (by Dr. S. Mikkelsen) at $[Br^-]$=0.10, 0.05, and 0.01M gave the values of 'K_B' = 0.126, 0.202 and 0.587 mM, respectively, for the apparent binding of Br_2 to CD. The trend to higher values at low $[Br^-]$ is also consistent with stronger binding of Br_3^- to CD (compared to

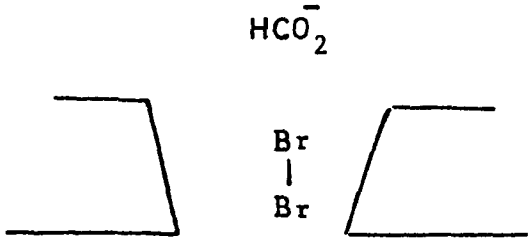
that of Br_2), which becomes less important at low [$\bar{Br}$]. In other words, the variation of [Br_2] with]CD] is governed largely by the formation of the CD.$\bar{Br_3}$ complex.

Considering the question of the catalysis by the CD.Br_2 complex, the data are analyzed on the basis of reaction model 'A' (eq.23) ignoring the very weak binding of the substrate with α-CD.[30]

$$k_2^{app}/f_B = k_2 + k_2^A[CD]/K_B$$

Table XX shows the rate constants calculated based on model 'A', for formic acid at two pHs. These results show CD.Br_2 to be 11 times more reactive than Br_2 towards $H\bar{C}O_2$ in the oxidation reaction.[37]

On the basis of the above analysis, and neglecting the weak binding of CD.$H\bar{C}O_2$, it can be safely said that the catalysis of the reaction involves the attack of complexed bromine on free substrate (model 'A'), Scheme 6.



Scheme 6

Table XX. Rate constants evaluated for the reaction model 'A' for formic acid at two different pHs.[a]

pH	k_2 $M^{-1}s^{-1}$	$k_2^A=k_3K_B$ $M^{-1}s^{-1}$	k_2^A/k_2	K_{TS} mM
2.08	0.942	10.7	11.4	0.19
5	31.7	368	11.6	0.18

The above reaction model is also supported by an estimation of the dissociation constant of the transition state, K_{TS} which reflects the binding of the oxidation transition state to CD[36] (Table XX): K_{TS} = 0.19 and 0.18 for formic acid at two pHs. Similar K_{TS} values have been found for the reaction of bromine with phenols.[10]

CHAPTER 7

CONCLUSION

Significant rate changes exhibited in the bromination of a variety of organic substrates in the presence of α-cyclodextrin support the remarkable role of α-CD as a catalyst in these reactions.

Steric and reactivity arguments favour a non-covalent mechanism involving the reaction of free substrate with complexed bromine. The present results explain this behaviour, quite well for phenols, salicylate anions, pyridones and formic acid. Aromatic and heteroaromatic carboxylate anions, however, show slight deviation from this behaviour. This may indicate a different manner by which the bromination of these compounds takes place in the presence of α-CD.

The present study on the rates of bromination of the above substrates in the presence of α-CD is consistent with a reaction transition state in which the α-CD-Br_2 complexation carries the catalytic importance. It is argued that in the transition state the two bromine atoms involved are mainly in the CD cavity whereas the organic moiety with its substituents is essentially outside of the cavity in a largely aqueous environment. Hence, the substituent effects for the catalyzed and uncatalyzed reactions are very similar.

CHAPTER 8

EXPERIMENTAL

8.1 MATERIALS

Most of the substrates and α-cyclodextrin used were of commercial origin and were obtained from Aldrich. The impure compounds were purified by recrystallization. The list of compounds which were recrystallized or synthesized together with their melting points are given in Table XXI.

m-Nitrophenyl acetate was obtained from M. Bozzi.

8.2 PREPARATION OF SOLUTIONS

a: Bromine Solutions. These were prepared by dilution of a small volume of a stock solution (0.1M in 0.1M KBr) with water. The parent solution was made by weighing a small amount of liquid bromine into 10 mL of 0.1M KBr and diluting to the required concentration with buffer solution containing 0.1M KBr. For all the bromination experiments the concentration of bromine was $5x10^{-5}$ M (after mixing in the stopped-flow apparatus). The solutions were used within few hours of preparation.

b: Cyclodextrin Solutions. Aqueous stock solutions of α-CD at fixed pH and ionic strength were used within 24 hours of preparation. For most of the bromination experiments, the concentrations of α-CD were 1-5 mM. For inhibition kinetics [α-CD] was 1mM.

Table XXI. List of compounds synthesized or recrystallized and their melting points.

Serial Number	Compound	M.Pt (°C)
1	5-Bromosalicylic acid[a]	163-165
2	2-Furoic acid[a]	128-130
3	3-Furoic acid[a]	122-125
4	2-Thiophene carboxylic acid[a]	127-130
5	p-Anisic acid[b]	181-185
6	2-Pyridone[c]	106-107
7	1-Methyl-2-Pyridone[d]	
8	4-Pyridone[e]	
9	1-Methyl-4-Pyridone[f]	

[a] recrystallized from water.

[b] recrystallized from chloroform.

[c] recrystallized from a mixture (2:1) of petroleum ether and benzene.

[d] for solubility reasons, the hydrobromide salt was used which was made as follows:
1-Methyl-2-Pyridone was reacted with a slight excess of concentrated HBr (48%) in acetone. The solution was evaporated by heating and recrystallized from a mixture (1:3) of methanol and acetone. The crystals had melting point range of 175-177°C.

[e] The nitrate salt used was synthesized by M. Paventi.[27]

[f] The hydrobromide salt used, was prepared by M.Paventi.[27]

c: Buffer Solutions. Except for phenols and formic acid, the bromination kinetics for rest of the compounds was carried out at pH 5. For these, sodium acetate/acetic acid buffer (0.1M) was prepared according to Perrin.[38] For phenols and formic acid for higher acidity (pH 1 or 2) dilute aqueous HCl was used. The ionic strength of all the above solutions were kept constant with 0.1M KBr.

For bromide ion dependence studies, the ionic strength was maintained by the addition of NaCl.

For inhibition kinetics a phosphate buffer (0.4M) of pH 11.6 was prepared by following the Perrin's[38] recipe.

d: Substrate Solutions. Except for phenols, the stock solutions (0.01-0.05M) of all the substrates were made in aqueous buffer (pH 5) for the bromination experiments. For phenols the stock solutions (0.1-0.5M) were prepared in analytical grade methanol for solubility reasons.

Except for p-anisic acid (10^{-3} M) and formic acid (0.1M) the concentration of all the substrates is $5x10^{-4}$ M.

For inhibition experiments all stock solutions were made in water. The concentrations of these solutions vary for each inhibitor. For very high concentration of the stock solution, the solutions were placed in ultrasonic bath to assist the dissolution. Where the inhibitor was an acid, the stock solution was neutralized with a base (NaOH).

e: MNPA Solution. The stock solution (0.1M-0.2M) of the substrate (m-nitro phenyl acetate) for the inhibition kinetics

was made in analytical grade methanol. For all the inhibition experiments, the concentration of the ester is $2x10^{-4}$ M.

8.3 KINETIC STUDIES

a: Bromination

The kinetics of bromination were examined using an Aminco DW-2 UV-visible spectrophotometer operating in the dual beam together with a stopped-flow accessory.[39] The cell was thermostated at 25°C±0.1°C. The stopped-flow experiments involved the mixing of equal volumes of CD/substrate in buffer (syringe #1) with a bromine/buffer solution (syringe #2). With a ten-fold excess of substrate over bromine pseudo first-order kinetics were monitored by the decrease in the absorbance at 265-285nm due to the tribromide ion.

The absorbance data were analyzed by an Apple II microcomputer which was interfaced to the spectrophotometer via a Cyborg Isaac 91a. Least squares analysis of $\ln (A_t - A_{inf})$ versus time showed good linearity ($r \geq 0.999$). Each reported first-order rate constant (k^{obs}) is an average of at least four individual runs. The k^{obs} were then converted to apparent second-order rate constants by division by $(S)_o-(Br_2)_o$ for reasons given elsewhere.[40]

b: Inhibition

The kinetics of cleavage of m-nitrophenyl acetate ester (MNPA) was measured by monitoring the appearance of the phenoxide ion at λ_{max} 405 nm. A solution containing aqueous

buffer and CD (1mM) was mixed (1:1) with an aqueous solution of MNPA ($2x10^{-4}$ M) and various concentrations of the inhibitor in the stopped-flow apparatus attached to an Aminco DW-2 UV-vis spectrophotometer. All kinetic runs were done at 25°C±0.1°C. Under the conditions studied, phenoxide appearance showed good pseudo first-order behaviour for more than 90% reaction.

The rate constants (k^{obs}) were determined from the slope of $\ln(A_{inf}-A_t)$ vs time. The final absorbance value (A_{inf}) was measured after ten half lives (>99.9% reaction).

8.4 TREATMENT OF DATA

The computer programs used in this study are CDFIT and INHIB. These were written in TURBOPASCAL by Tee, O.S. and Takasaki, B. CDFIT has two basic options for data analysis:

1. Linear least squares fitting to eq.14 which allows for the dependence of k_2^* on [CD] at fixed (given) K_s value. Non-linear fitting of k_2 and k_3 in eq.13, with K_s fixed.
2. Estimation of K_s using a Eadie-Hofstee type of analysis (Chapter 6). Also, non-linear least squares fitting to eq.13, with k_2, k_3, and K_s as the parameters.

The INHIB program is based on eq.15, which allows the determination of the dissociation constant of the inhibitor-CD from the intercept of a plot of $[I_o]$ vs $(k_c-k^{obs}) / (k^{obs}-k_u)$.

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APPENDIX

(TABLES A-I TO A-VI)

Table A-I. Apparent second-order rate constants (k_2^{app}, $M^{-1}s^{-1}$) for the bromination of phenols (pH 1) and salicylate anions (pH 5) as a function of α-cyclodextrin concentration.[a]

Phenols

	k_2^{app}, $M^{-1}s^{-1}$		
[CD]	p-F-	p-Cl-	p-I-
mM	1a	1b	1d
0	1560	1300	1990
1	1300	818	844
2	1200	620	473
3	1120	513	318
4	1100	449	240
5	1020	396	204

Salicylates

	k_2^{app}, $M^{-1}s^{-1}$		
[CD]	5-Br	$5\text{-}SO_3^-$	$5\text{-}NO_2$
mM	1e	1f	1g
0	5.45×10^4	3.95×10^4	5.79×10^3
1	5.40×10^4	2.46×10^4	2.75×10^3
2	4.37×10^4	1.99×10^4	1.99×10^3
3	4.25×10^4	1.87×10^4	1.71×10^3
4	3.92×10^4	1.80×10^4	1.51×10^3
5	3.49×10^4	1.65×10^4	1.41×10^3

[a] $[S]=5\times10^{-4}M$ $[Br_2]=5\times10^{-5}M$.

[Br] = 0.1 M

Table A-II. Apparent second-order rate constants (k_2^{app}, $M^{-1}s^{-1}$) for the bromination of carboxylate anions as a function of α-cyclodextrin concentration at pH 5.

Heteroaromatic carboxylate anions

$[CD]_t$ mM	2a 2-Furoate	2b 3-Furoate	2c 2-Thiophene
0	8333	1.88×10^4	484
1	3133	8733	179
2	1971	6244	106
3	1611	5244	76.4
4	1453	4733	65.3
5	1331	4533	55.5

Aromatic carboxylate anions

$[CD]_t$ mM	2d Phenoxy acetate	2e 2-Phenoxy propionate	2f 2-Anisate	2g[a] 4-Anisate
0	5622	1.06×10^4	1964	66.3
1	2178	3622	696	27.8
2	1378	2244	418	17.8
3	978	1629	351	12.3
4	800	1298	242	9.53
5	689	1144	209	8.71

[a] [S] is 10^{-3} M; for rest of the compounds [S]=5×10^{-4} M; $[Br_2]=5 \times 10^{-5}$ M; [Br]=0.1M.

Table A-III. The observed and calculated apparent second-order rate constants for the CD-mediated bromination of pyridones.[a]

	2-Pyridone		$N\text{-}CH_3$-2-Pyridone	
[CD]	$k_2^{app}, M^{-1}s^{-1}$		$k_2^{app}, M^{-1}s^{-1}$	
mM	obs	calc	obs	calc
0	6489	6480	12422	12413
1	2822	1535	3667	2311
2	2084	822	2222	757
3	1764	541	1616	603
4	1613	391	1298	395
5	1560	301	1120	280

	4-Pyridone		$N\text{-}CH_3$-4-Pyridone	
[CD]	$k_2^{app}, M^{-1}s^{-1}$		$k_2^{app}, M^{-1}s^{-1}$	
mM	obs	calc	obs	calc
0	3268	3268	3422	3422
1	1633	775	1191	543
2	1289	415	760	226
3	1084	274	558	125
4	1042	197	451	79
5	997	152	389	54

[a] The calculated values are based on eq. 12.

Table A-IV. Pseudo first-order rate constants as a function of the inhibitor concentration for salicylates[a] (1e and 1f).

5-Br (1e)		5-SO_3 (1f)	
[I] mM	k^{obs} s^{-1}	[I] mM	k^{obs} s^{-1}
0	0.718	0	0.775
1	0.615	4	0.705
2	0.517	8	0.654
3	0.459	12	0.606
4	0.423	16	0.566
5	0.388	--	-----

[a] All measurements done at pH 11.6, [Ester]=2×10^{-4} M, [CD] = 1mM.

Table A-V. Pseudo first-order rate constants as a function of the inhibitor concentration for carboxylates.[a]

a: Heteroaromatic carboxylate anions

2-Furoate		3-Furoate		2-Thiophene	
[I] mM	k^{obs} s^{-1}	[I] mM	k^{obs} s^{-1}	[I] mM	k^{obs} s^{-1}
0	0.812	0	0.778	0	0.796
20	0.649	10	0.728	10	0.683
40	0.554	20	0.643	20	0.584
60	0.473	30	0.582	30	0.543
80	0.403	40	0.534	40	0.509
100	0.356	50	0.513	50	0.473

b: Aromatic carboxylate anions

Phenoxy acetate		2-Phenoxy propionate		2-Anisate		4-Anisate	
[I] mM	k^{obs} s^{-1}	[I] mM	k^{obs} s^{-1}	[I] mM	k^{obs} s^{-1}	[I] mM	k^{obs} s^{-1}
0	0.778	0	0.739	0	0.754	0	0.777
20	0.608	10	0.647	10	0.717	5	0.714
40	0.495	20	0.575	20	0.674	10	0.635
60	0.429	30	0.542	30	0.616	15	0.583
80	0.368	40	0.484	40	0.592	20	0.528
--	---	50	0.449	50	0.548	25	0.479

[a] For all the above experiments pH=11.6, [Ester]=2×10^{-4} M, [CD] = 1mM.

Table A-VI. Pseudo first-order rate constants for the oxidation of formic acid.[a]

[CD] mM	k_1^{obs} s^{-1} pH 2.08	pH 5
0	0.0339	0.114
1	0.0429	0.157
2	0.0428	0.160
3	0.0430	0.154
4	0.0466	0.157
5	0.0451	0.158

[a] [S]=0.1M, $[Br_2]=5x10^{-5}$ M, [Br]=0.1M.