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ELECTROPHILIC CATALYSIS BY CYCLODEXTRINS

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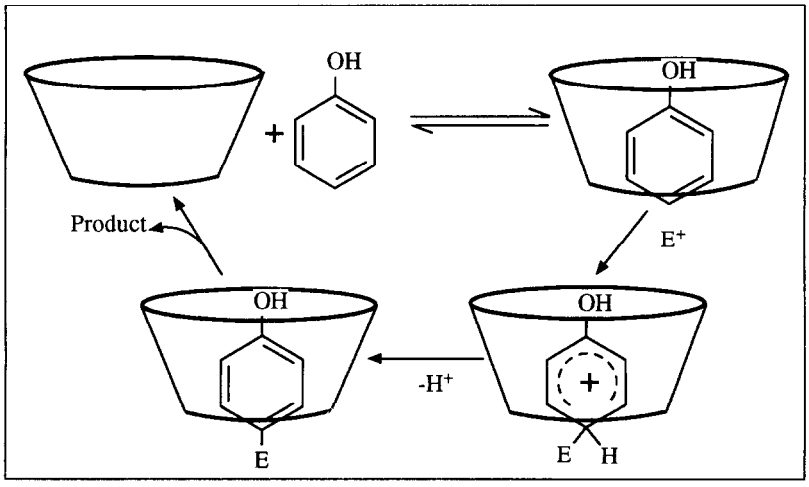
Abstract: The catalysis of an aromatic electrophilic substitution reaction by cyclodextrins is reported. The catalysis can be explained on the bases of the electron rich character of the interior of the cyclodextrin cavity. Kinetic analyses of this reaction in the presence of cyclodextrins indicate binding and catalysis.

Cyclodextrins, cyclic oligomers consisting of 6 (in α), 7 (in β) and 8 (in γ) glucose units linked together in α-1,4 linkages, have attracted substantial attention in the last decade because of their ability to complex small organic molecules and catalyze various reactions.[1] Most of the reactions catalyzed by cyclodextrins have been categorized as either covalent catalysis, conformational catalysis, or microsolvent catalysis.[2] It is well known that the glycosidic oxygens within the cavity of cyclodextrins have their lone pairs of electrons pointing towards the inside of the ring, thus making the cavity Lewis basic in character.[3] Cavities of modified cyclodextrins have been known to provide a suitable environment for binding metal ions.[4] If the electron rich environment of the cavity could stabilize an electron deficient species formed as an intermediate in a reaction, the transition-state energy would be lowered and thus the reaction would be catalyzed. This idea can be explored in an aromatic electrophilic substitution reaction.



Scheme 1: Catalysis of an aromatic electrophilic reaction by cyclodextrins.

Aromatic rings are known to bind to cyclodextrin with dissociation constants ranging from 10^{-2} to 10^{-3} M depending on the nature of the substituents on the ring.[5] If the aromatic rings thus bound to cyclodextrins were to undergo an electrophilic substitution reaction, it would produce a cationic intermediate (the sigma complex) with a positive charge delocalized over the benzene ring. This electron deficient species may be stabilized by the electron rich environment of the cyclodextrin cavity as shown in Scheme 1. The electrophilic substitution reaction investigated for this purpose was the coupling of a diazonium salt with phenol. An earlier examination of this reaction by Breslow[6] using *p*-diazoniumbenzenesulphonate and phenol in the presence of α-cyclodextrin led to the conclusion that the electrophile did not attack the cyclodextrin-bound substrate.

The reactions reported here were carried out at *p*H values where cyclodextrins did not form diazotates[7] with the diazonium salts. Under the reaction conditions, a single product was formed and it was verified to be identical to the product in the absence of cyclodextrin. A typical reaction mixture contained 3 x 10^{-4} M phenol dissolved in 3 ml of *p*H 7.0 aqueous buffer. To this solution was added a 30 µl aliquot of a stock solution of the phenyldiazonium chloride so that the final concentration of the diazonium salt in the reaction mixture was 5 x 10^{-5} M. The concentrations of α- and β-cyclodextrins were varied between 1 x 10^{-1} M to 3 x 10^{-3} M (0.2 K_d to 2 K_d). The electrophilic coupling reaction was assayed by observing the increase in the absorbance at 355 nm due to the formation of the product using a Varian 2215 spectrophotometer with a thermostated cell holder maintained at 0°C. The data were collected electronically for at least 5 half lives and the first order rate constants were calculated using the Enzfitter[8] program. The rate constants were confirmed from the half lives of the reactions.

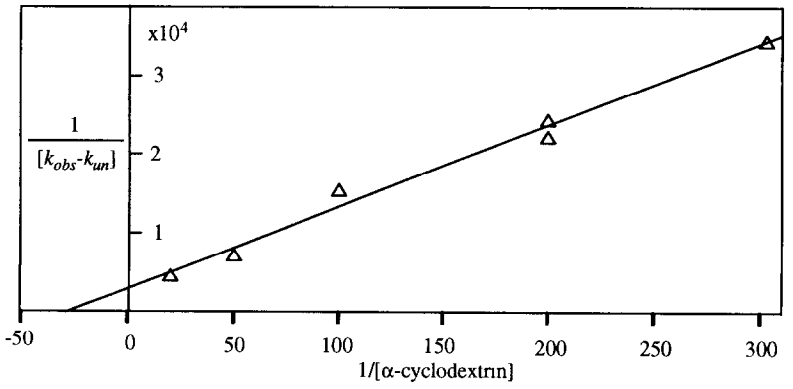


Figure 1: A double reciprocal plot of the observed pseudo first order rate constants corrected for uncatalyzed reaction *versus* the concentration of cyclodextrin.

Kinetic analysis of the results in the reaction between *p*-chlorophenyldiazonium chloride and phenol in the presence of α- and β-cyclodextrins were carried out using a variant of the Lineweaver-Burk equation[9] as

prescribed in the literature[5]. Figure 1 is a plot of $1/(k_{obs}-k_{un})$ *versus* 1/[CD] which is linear with k_{cat}[10] as the **Y** intercept and $-1/K_{diss}$ as the **X** intercept. The kinetic constants for the above reactions are given in Table I.

Table 1: Rate constants for the reaction between *p*-chlorophenyldiazonium salt and phenol catalyzed by α- and β-cyclodextrins.

CD	k_{cat} $10^{-4}\ s^{-1}$	K_{diss} $10^{-2}\ M$
α	3.4 ± 1.2	3.6 ± 1.3
β	4.2 ± 0.96	1.6 ± 0.37

The "saturation kinetics" represented in figure 1 indicate that the reaction proceeds via formation of a complex and the dissociation constants observed here are similar to the ones reported in the literature (2 2 x 10^{-2} M for phenyl acetate and β-cyclodextrin).[5] The first order rate constant for the electrophilic substitution reaction under this investigation in water under identical reaction conditions (k_{un}) was found to be 1.5 x 10^{-4} s^{-1} which is 2.8 times smaller than the first order rate constant for the same reaction in the β-cyclodextrin cavity. This is interesting because water can provide stabilization to the transition state through its non-bonded electrons on the oxygen in the same way as does cyclodextrin. The increased rate of the reaction within the cavity of cyclodextrin can be explained through the lower entropy and solvent reorganization energy involved within the cyclodextrin cavity compared to water mediated reaction.

Although we have not presented any direct evidence for the involvement of the glycosidic oxygens within the cavity in the electrophilic catalysis by cyclodextrin as proposed here earlier, the data presented herein clearly suggest the participation of the cyclodextrin cavity. It is reasonable to expect the glycosidic oxygens to interact with the cationic intermediate in a fashion similar to the interaction of cations with crown ethers. Such an interaction is expected to facilitate the reaction by stabilizing the intermediate. An alternate explanation for this effect, analogous to an earlier report[11], is that the electrophilic attack is on the phenoxide ion and the intermediate is a neutral species which is stabilized by the hydrophobic cavity of cyclodextrin more than the phenoxide ion. However, there is no evidence that the cyclodextrin cavity can bind a neutral species better than a negatively ionized species especially in view to the fact that the phenoxide ions bind to cyclodextrins *ca*

Table 2: The effect of cyclodextrins on the first order rate constants in the reaction between substituted phenyldiazonium salts and phenol[a].

R[b]	CD[c]	k_{obs}/k_{un}
$-SO_3^-$	α	1.02 ± 0.016
$-SO_3^-$	β	1.87 ± 0.011
-Cl	α	1.66 ± 0.046
-Cl	β	2.12 ± 0.066
$-OCH_3$	α	1.60 ± 0.037[d]
$-OCH_3$	β	5.94 ± 0.135[d]

[a] conditions same as described earlier; [b] R = substituent at the *p*-position of the phenyldiazonium salt; [c] [CD] = 0.01M; [d] at *p*H 10.0.

10 times better than neutral phenols.[6]

As indicated in table 2, α- and β-cyclodextrins have a real effect on the rate of electrophilic attack of diazonium salt on phenol with an exception of the earlier examined[6] reaction of *p*-diazoniumbenzenesulphonate with phenol in the presence of *α-cyclodextrin*. The interactions between α-cyclodextrin and the sulphonate appear to inhibit the attack of the diazonium salt on to the bound phenol.

Cationic intermediates are fairly common in organic chemistry and several electrophilic reactions have been known to be catalyzed by cyclodextrins.[6,11,12] These have been explained without invoking the participation of the Lewis basic character of the cyclodextrin cavity. If the effect presented here can be extrapolated to these systems, it is possible that the lone pairs of electrons in the cavity of cyclodextrin may be contributing to the catalysis of some of these systems.

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10. k_{un}, k_{obs} and k_{cat} are pseudo first order rate constants for the reaction in buffer; in the presence of cyclodextrins and of the cyclodextrin-bound substrate respectively. K_{diss} is the dissociation constant for cyclodextrin-phenol complex.
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