Catalysis of the Bromination of Phenols and Phenoxide Ions in Aqueous Solution by α-Cyclodextrin

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Abstract: α-Cyclodextrin (CD) causes slight accelerations or retardations in the bromination of nine phenols and six phenoxide ions. Since CD forms fairly strong complexes with Br_2, Br_3^-, and phenols, large rate reductions should be observed if the only reaction occurring involved *free* bromine reacting with *free* substrate. Thus, the results are consistent with a bromination pathway that is catalyzed by CD, and analysis of the kinetics shows that the reaction involves bromine, substrate, and *one* molecule of the cyclodextrin. Two pathways are plausible: A, reaction between *free* substrate and the bromine·CD complex; B, attack of *free* bromine on the substrate·CD complex. Substituent effects are more consistent with pathway A: for phenols ρ^+ is virtually the same for the catalyzed and normal reactions and there are only small differences in the catalysis of 2- and 4-substituted derivatives; for phenoxide ions both reactions are diffusion controlled, the rate being slightly higher for the catalyzed reaction.

Simple phenols react with aqueous bromine directly or via their anions, depending on the pH.[1-3] Also, phenols and phenoxide ions form host–guest complexes with α-cyclodextrin (CD)[4] in which the meta and para positions of the phenol reside within the hydrophobic cavity of the cyclodextrin host.[4,5] Since bromine also forms a complex with CD,[6] we expected that CD would exert significant effects on the normal course of phenol bromination.

Initial kinetic experiments showed that several factors are involved. In order to clarify these we carried out a detailed study of the effect of CD on the bromination of two anisoles.[7] These substrates lack an ionizable group and so fewer equilibria and mechanistic possibilities needed to be considered. Even so, it was found that *five equilibria* are important: tribromide ion formation[1,3] and the complexations of CD with tribromide ion,[7] bromine,[6] bromide ion,[8] and the anisole.[6]

For *p*-methylanisole bromine attack is greatly retarded by CD due to the reductions in the concentrations of free bromine and free substrate caused by the equilibria noted above. However, for unsubstituted anisole the rate reduction is much less, and analysis of the rate data indicated the presence of a bromination pathway involving one molecule of CD.[7]

We now report on a detailed study of the effect of CD on the rates of bromination of several phenols and phenoxide ions. The results indicate a reaction pathway in which CD catalyzes bromine attack.

Results

The kinetics of bromination of various phenols in aqueous solutions containing CD have been studied by using established stopped-flow techniques.[3,7,9] Before presenting our results, we review the equilibria that must be taken into consideration.[7]

Equilibria. Bromination reactions in water are most conveniently studied by using an excess of Br^- and by monitoring the decrease in absorbance due to the tribromide ion.[9a] This ion is formed in a fast equilibrium:[10]

$$Br_3^- \rightleftharpoons Br_2 + Br^-; \qquad K = 0.0562\ M^{11} \tag{1}$$

For an excess of Br^- the fraction of free Br_2 is

$$f_B = K/(K + [Br^-]) \tag{2}$$

All three species in the equilibrium form complexes with CD:

$$CD{\cdot}Br^- \rightleftharpoons CD + Br^-; \qquad K_1 = 0.286\ M^8 \tag{3}$$

$$CD{\cdot}Br_2 \rightleftharpoons CD + Br_2; \qquad K_B = 2.1\ mM^6 \tag{4}$$

$$CD{\cdot}Br_3^- \rightleftharpoons CD + Br_3^-; \qquad K_T = 0.17\ mM^7 \tag{5}$$

The complexation of Br^- is weak but it cannot be ignored since $[Br^-]$ is high and it affects the amount of CD that is available for the complexation of other species. This quantity is given by

$$[CD] = [CD]_t K_1/(K_1 + [Br^-]) \tag{6}$$

where $[CD]_t$ is the total CD concentration. In all subsequent data analysis the CD concentration given by eq 6 is used.

When CD is present the amount of free bromine is sharply reduced due to the effects of the equilibria shown in eq 1, 4, and 5. Correcting for these[7,12]

$$f_B = KK_BK_T/(K_BK_T(K + [Br^-]) + [CD](KK_T + K_B[Br^-])) \tag{7}$$

The formation of phenol–CD complexes is easily corrected for by taking the fraction of free substrate as[12]

$$f_S = [S]/[S]_t = K_S/(K_S + [CD]) \tag{8}$$

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

Kinetics. The reaction of phenols with aqueous bromine exhibits second-order kinetics,[1-3] even though cyclohexadienones can be observed in some cases.[3c,13] In the presence of Br^- the apparent rate constant (k_2^{app}) is reduced relative to the actual rate constant

$$S + Br_2 \xrightarrow{k_2} \text{products} \tag{9}$$

(k_2) due to the formation of Br_3^- (eq 1);[1] it is given by[14]

$$k_2^{app} = k_2 f_B \tag{10}$$

where f_B has the form in eq 2. When CD is also present, k_2^{app} should be greatly decreased due to reductions in the free bromine

(1) Bell, R. P.; Rawlinson, D. J. *J. Chem. Soc.* **1961**, 63.
(2) Kulic, J.; Vecera, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 71.
(3) (a) Tee, O. S.; Iyengar, N. R.; Kraus, B. *J. Org. Chem.* **1985**, *50*, 973. (b) Tee, O. S.; Iyengar, N. R. *J. Org. Chem.* **1985**, *50*, 4468. (c) Tee, O. S.; Iyengar, N. R.; Paventi, M. *J. Org. Chem.* **1983**, *48*, 759. (d) Paventi, M. Ph.D. Thesis, Concordia University, Montreal, 1984. (e) Tee, O. S.; Paventi, M.; Iyengar, N. R.; Bennett, J. M., manuscript in preparation.
(4) Bender, M.; Komiyama, M. *Cyclodextrin Chemistry*; Springer Verlag: New York, 1978.
(5) (a) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. (c) Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Eds. *Inclusion Compounds*; Academic Press: London, 1984; Vol. 2, Chapter 8; Vol. 3, Chapter 12. (d) Matsui, Y.; Nishioka, T.; Fujita, T. *Topics Curr. Chem.* **1985**, *128*, 61.
(6) Breslow, R.; Campbell, P. *Bioorg. Chem.* **1971**, *1*, 140.
(7) Tee, O. S.; Bennett, J. M. *Can. J. Chem.* **1984**, *62*, 1585.
(8) Wojcik, J. F.; Rohrbach, R. P. *J. Phys. Chem.* **1975**, *79*, 2251. This reference was inadvertantly left out of ref 7.
(9) (a) Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830. (b) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.
(10) Ruasse, M.-F.; Aubard, J.; Galland, B.; Adenier, A. *J. Phys. Chem.* **1986**, *90*, 4382.
(11) Bell, R. P.; Ramsden, E. N. *J. Chem. Soc.* **1958**, 1294.
(12) Equations 7 and 8 assume that $[CD]_t > [Br_2]$ and [phenol], as was generally the case.
(13) (a) Tee, O. S.; Iyengar, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 455. (b) Tee, O. S.; Iyengar, N. R.; Bennett, J. M. *J. Org. Chem.* **1986**, *51*, 2585. (c) Tee, O. S.; Iyengar, N. R. *Can. J. Chem.* **1987**, *65*, 1714.

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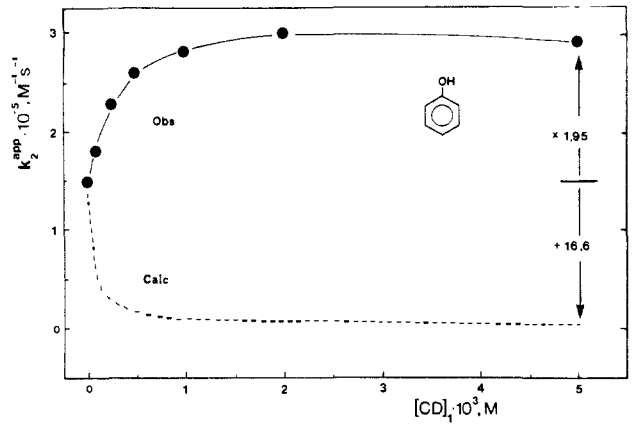


Figure 1. Variation of k_2^{app} for the bromination of phenol with total concentration of α-cyclodextrin (in 0.1 M KBr at pH 1.84). The dashed line, calculated from eq 11, is the expected curve if the only significant reaction involved attack of *free* bromine on *free* phenol. Similar data were obtained in 0.05 M KBr (+0.05 M NaCl) and for other phenols (Table S3).

and free substrate; the expected form of the rate constant then is[14]

$$k_2^{app} = k_2 f_S f_B \quad (11)$$

where f_S can be taken from eq 8 and f_B now has the more complex form given in eq 7.

The effect of CD on the kinetics of bromination of *p*-methylanisole is completely explained by eq 11.[7] However, for unsubstituted anisole[7] (and the present substrates) values of k_2^{app} are very much greater than expected from eq 11.

For the bromination of phenol in 0.1 M KBr at pH < 4 values of k_2^{app} (Table S1, Supplementary Material) are constant, with an average of 154 000 M^{-1} s^{-1}.[15] However, in the presence of 5 mM CD, the average is 318 000 M^{-1} s^{-1}. Thus, k_2^{app} is *increased* by the presence of CD; *it is not substantially reduced* in the manner prescribed by eq 11.

An example of the variation of rate with $[CD]_t$ is shown in Figure 1. The value of k_2^{app} *increases* until at $[CD]_t$ = 5 mM it is twice its initial value whereas the expected value of k_2^{app}, from eq 11, is *decreased* by a factor of 17 (Figure 1). Therefore, *there is a CD-catalyzed pathway that more than makes up for the suppression of the normal reaction* of bromine with phenol.

As an initial approach to analyzing the data we consider a contribution from a process involving substrate, bromine, and *one* molecule of CD:[16]

$$S + Br_2 + CD \xrightarrow{k_3} \text{products} \quad (12)$$

If such a process is involved, k_2^{app} has contributions from the normal bromination (eq 9) and this additional process and so

$$k_2^{app} = (k_2 + k_3[CD]) f_S f_B \quad (13)$$

This equation has a nonlinear dependence on [CD] because of the forms of f_S and f_B (eq 7 and 8). It is, therefore, convenient to rearrange eq 13 and define a constant (k_2^*) with a linear dependence on [CD]:

$$k_2^* = k_2^{app}/f_S f_B = k_2 + k_3[CD] \quad (14)$$

In essence, this procedure corrects k_2^{app} for the depletion of free substrate and free bromine.

Figure 2 shows the plot based on eq 14 for the raw data in Figure 1; it is linear (r = 0.9998) with a slope of $k_3 = 3.52 \times 10^9$ M^{-2} s^{-1}. Data obtained at a lower $[Br^-]$ (=0.05 M) gave a similar slope of 3.36×10^9 M^{-2} s^{-1} (r = 0.9999). The linearity of the plots validates the use of eq 14 and indicates that the calculations of f_S and f_B are successful.[17]

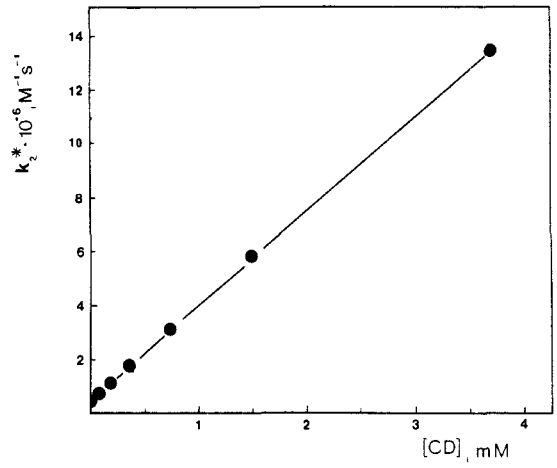


Figure 2. Plot of k_2^* vs [CD] for the raw data shown in Figure 1. The [CD] is corrected for the presence of bromide ion by the use of eq 6. Similar straight lines were obtained for other phenols (Table S3) and for reaction via phenoxide ions (Tables S4 and S5).

Table I. Rate Constants for the Aqueous Bromination of Phenols and Phenoxide Ions in the Presence of α-Cyclodextrin[a]

substrate	pK_a	k_2, M^{-1} s^{-1}	k_3, M^{-2} s^{-1}
		Phenols	
H		4.11×10^5	3.52×10^9 [b]
2-Me[c]		1.47×10^6	2.17×10^{10}
2,6-Me_2		1.20×10^6	1.17×10^{10}
2-Br[d]		1.01×10^4	6.72×10^7
4-Me		6.59×10^5	2.37×10^9
4-*t*-Bu		5.86×10^5	8.87×10^8
4-Br[d]		3890	8.54×10^6
4-COOEt[e]		1550	3.35×10^6
4-CN[e]		155	4.41×10^5
		Phenoxides[f]	
2-NO_2	7.12	1.60×10^9	5.74×10^{12}
2-Br	8.31	6.17×10^9	7.86×10^{12}
3-NO_2	8.24	4.18×10^9	2.81×10^{13}
4-NO_2	7.03	1.18×10^9 [g]	4.75×10^{12} [g]
4-Br	9.36	5.35×10^9 [h]	1.98×10^{13}
4-CN	7.84	3.13×10^9	5.79×10^{12}

[a] At 25 °C, in 0.01 M HCl (or buffer) + 0.10 M KBr (I = 0.11 M), unless noted otherwise. Values of k_2 were measured directly. [b] A value of $k_3 = 3.36 \times 10^9$ M^{-2} s^{-1} was obtained in 0.05 M KBr + 0.05 M NaCl. [c] Medium contained 1.0 M KBr. [d] In 0.10 M HCl + 0.10 M KBr. [e] In 1.0 M HCl + 0.10 M KBr. [f] Values of pK_a (I = 0.1 M) are taken from the literature or corrected from thermodynamic values. [g] Similar values were obtained at other pHs and other $[Br^-]$ (see Table S4). [h] Half the observed value which is elevated due to dibromination.[3d,3e]

Tribromide ion forms a strong complex with CD[7] (eq 5) which might be involved in the CD-mediated pathway. However, for phenol and *p*-cresol, values of k_2^* at fixed [CD] show no dependence on $[Br^-]$ (Table S2), inconsistent with the involvement of Br_3^- in any form. Likewise, the closeness of the slopes of k_2^* vs [CD] found at $[Br^-]$ = 0.10 and 0.05 M (previous paragraph) militates against such involvement.

The variations of k_2^{app} with $[CD]_t$ have been determined for nine phenols (Table S3) at pHs where reaction normally occurs on the undissociated forms.[1-3] For five of the phenols there are modest rate increases; for the remainder the rates decrease but *in no case* is the decrease as large as that required by eq 11. As with phenol, the plots of k_2^* vs [CD] are linear (Table S3), consistent with the model expressed by eq 12–14. The slopes of

(14) This assumes there is no significant contribution from Br_3^- acting as the electrophile. Such is true for phenols but it is not necessarily true for very reactive phenoxide ions.[1,3]

(15) This, after correction for Br_3^- formation, gives k_2^{obsd} = 428 000 M^{-1} s^{-1}, in good agreement with other work.[3c-e]

(16) In the presence of CD (and an excess of phenol) bromine decay is first order and k_2^{app} is invariant when [phenol] is doubled (Table S2). Thus, the transition state contains substrate and bromine, as well as CD.

(17) This success is reassuring since the constants required for the calculations of k_2^* are taken from different sources.

these plots (k_3) are presented in Table I together with values of k_2 ($=k_2^{app}/f_B$ at zero [CD]).

Studies were also carried out on the effect of CD on the bromination of six phenols at pHs where they normally react via their anions.[1-3] Values of k_2^{app} decrease with $[CD]_t$ (Tables S4 and S5) but not as much as required by eq 11. For *p*-nitrophenol at different pHs and $[Br^-]$, plots of k_2^* vs [CD] are linear (Table S4) and the slopes increase with pH, consistent with reaction via the anion (see below). Also, the slopes do not vary with $[Br^-]$, indicating no involvement of Br_3^-. Similarly, no reaction with Br_3^- was detected for *m*-nitrophenoxide ion (Table S6), even though it showed the most catalysis of all the anions studied.

To take account of reaction via the phenoxide ion eq 14 must be modified to

$$k_2^* = (k_2 + k_3[CD])K_a/[H^+] \quad (15)$$

This equation is valid for the present conditions where $[H^+] \gg K_a$ and K_S(phenol) is not very different from K_S(phenoxide),[4,18-20] so that f_S may still be taken from eq 8.[21] Thus, a plot of k_2^* vs [CD] should be linear with the slope $= k_3K_a/[H^+]$. For the present data such plots are linear (Tables S4 and S5) and so the slopes were multiplied by the factor $[H^+]/K_a$ to yield the values of k_3 given in Table I.

Discussion

Our results show the existence of a pathway for the aqueous bromination of phenols and phenoxide ions which is mediated by CD. Before discussing plausible models for this reaction, we will consider and reject other possibilities.

Various studies in which $[Br^-]$ was varied failed to indicate any involvement of Br_3^- in the CD-catalyzed reaction. Likewise, the data are not consistent with reaction by way of HOBr or a cyclodextrin hypobromite ester.[22] The formation of such species is highly unfavorable under the reaction conditions[23] and the equilibria concerned

$$ROH + Br_2 \rightleftharpoons ROBr + H^+ + Br^- \quad (16)$$

require an inverse dependence on $[H^+]$ and $[Br^-]$, which is not observed.

In contrast, the data are compatible with a transition state composed of phenol (or phenoxide ion), bromine, and *one* molecule of CD (eq 12) and analysis gave the third-order rate constants, k_3. Whatever the significance of these constants, one thing is clear: there is a strong parallelism between the values of k_3 and k_2 (Table I).

For the reaction of phenols with bromine k_2 varies over a range of 10^4 while for the CD-catalyzed reaction the values of k_3 have a range of 5×10^4. For phenoxide ions the k_2 values are almost constant at the diffusion-controlled limit,[24] as expected from earlier work.[1-3] Likewise, the values of k_3 show little variation. Broadly speaking, therefore, the substituent effects in the catalyzed and uncatalyzed processes are very similar, which suggests that they do not differ markedly in a mechanistic sense.

Cyclodextrins may function as catalysts in two basic ways.[4] First, they may afford "covalent catalysis" in which there is a distinct covalent interaction between a functional group on the cyclodextrin and the reactant(s) at some point in the reaction. Such catalysis is strongly dependent on the position of the substituent on an aryl substrate.[4,5] However, the present data do not show any significant dependence of the catalysis on the substituent position (see later).

The second type of catalysis is "noncovalent"[4] and the cyclodextrin operates by providing an environment for reaction that is different from the bulk medium. The catalytic effect may be a microsolvent effect due to the less polar cavity of the cyclodextrin,[4] a geometric effect whereby encapsulation favors a reactive conformation,[4] or a consequence of complexation bringing two reactants together.[25] The attack of bromine on phenol[26] and other substrates[27] is much slower in less polar media and so a simple microsolvent effect is not consistent with the present results. Furthermore, space-filling (CPK) models indicate that it is physically impossible to include both Br_2 *and* a phenol in the cavity of a single CD molecule. Nevertheless, it is possible that CD catalyzes the reaction by facilitating the approach of the reactants, as has often been found for micellar catalysis.[28] The space

Scheme I

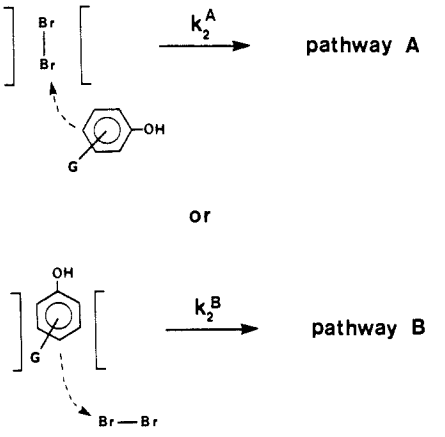


Table II. Rate Constants Evaluated for Two Reaction Models[a]

substrate	model A (eq 17A) $k_2^A = k_3K_B$	model A (eq 17A) k_2^A/k_2	model B (eq 17B) $k_2^B = k_3K_S$	model B (eq 17B) k_2^B/k_2
		Phenols		
H	7.4×10^6	18	1.8×10^8	440
2-Me	4.6×10^7	31	9.3×10^7	63
2,6-Me_2	2.5×10^7	21	1.8×10^7	150
2-Br	1.4×10^5	14	3.5×10^6	350
4-Me	5.0×10^6	7.6	2.0×10^8	300
4-*t*-Bu	1.9×10^6	3.2	6.2×10^6	11
4-Br	18000	4.6	12000	3.1
4-COOEt	7000	4.5	16000	10
4-CN	930	6.0	3100	20
		Phenoxides		
2-NO_2	1.2×10^{10}	7.5	$\sim 2.3 \times 10^{11}$	~140
2-Br	1.7×10^{10}	2.8	$\sim 8.6 \times 10^{11}$	~140
3-NO_2	5.9×10^{10}	14	1.2×10^{11}	29
4-NO_2	1.0×10^{10}	8.5	2.2×10^9	1.9
4-Br	4.2×10^{10}	7.9	2.4×10^{10}	2.2
4-CN	1.2×10^{10}	3.8	9.3×10^9	3.0

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

(18) (a) Gelb, R. I.; Schwartz, L. M.; Cardelino, B.; Fuhrman, H. S.; Johnson, R. F.; Laufer, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 1750. (b) Gelb, R. I.; Schwartz, L. M.; Cardelino, B.; Laufer, D. A. *Anal. Biochem.* **1980**, *103*, 362. (c) Van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.

(19) Connors, K. A.; Lipari, J. M. *J. Pharm. Sci.* **1976**, *65*, 379.

(20) Harata, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2737.

(21) For this not to be true, K_S(phenol) would have to be $>1000 \times K_S$(phenoxide) to offset the inequality $[H^+] \gg K_a$. Such is not the case (see Table III and Experimental Section).

(22) Chlorination of anisole using aqueous HOCl + CD involves a hypochlorite ester of the cyclodextrin.[6]

(23) (a) Pink, J. M. *Can. J. Chem.* **1970**, *48*, 1169. (b) The present conditions (pH < 4.5, $[Br^-] \sim 0.1$ M) are such that <1% of the total bromine exists as HOBr.[9a]

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

(25) Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816. Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* **1983**, *105*, 2018.

(26) In water the attack of bromine on phenol (Table I) is 71 000 times faster than in acetic acid (6.0 M^{-1} s^{-1}: de la Mare, P. B. D.; el Dusouqui, O. M. H.; Tillett, J. G.; Zeltner, M. *J. Chem. Soc.* **1964**, 5306).

(27) Taylor, R. In *Comprehensive Chemical Kinetics*; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Vol. 13, Chapter 1, p 113ff. de la Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, England, 1976. Ruasse, M.-F.; Dubois, J.-E. *J. Am. Chem. Soc.* **1975**, *97*, 1977. Ruasse, M.-F.; Lefebvre, E. *J. Org. Chem.* **1984**, *49*, 3210.

(28) Kunitake, T.; Shinkai, S. *Adv. Phys. Org. Chem.* **1980**, *17*, 435. Romsted, L. S. In *Surfactants in Solution*; Mittal, K. L., Lindman, B., Eds.; Plenum Press: New York, 1984; Vol. 2, Chapter 5. For a recent study of the bromination of alkenes in micelles, see: Lennox, R. B.; McClelland, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 3771.

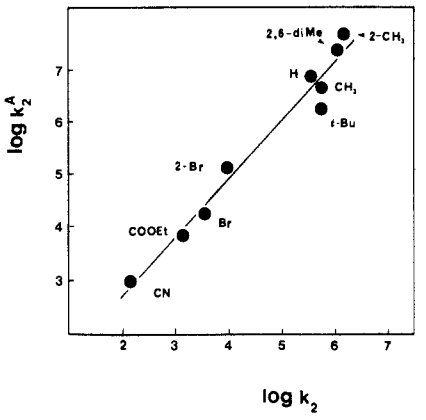


Figure 3. Plot of log k_2^A vs log k_2 for the bromination of phenols. The slope of 1.1 means that the CD-catalyzed (k_2^A) and normal (k_2) reactions have essentially the same ρ^+ values.[31] The analogous plot for k_2^B values shows more scatter.[32]

restriction simply means that when one of the reactants is in the CD cavity the other one must be outside. This type of model will now be considered in detail.

A strictly termolecular collision, as implied by the rate constant k_3 (eq 12), is highly unlikely. Much more probable is a bimolecular collision of one reactant with the CD complex of the other. Therefore, two possibilities must be considered:[29] pathway A, reaction between the *free* substrate and the CD–bromine complex (eq 17A); pathway B, attack by *free* bromine on the CD–substrate

$$S + CD + Br_2 \underset{K_B}{\rightleftharpoons} S + CD{\cdot}Br_2 \xrightarrow{k_2^A} \text{products} \quad (17A)$$

$$S + CD + Br_2 \underset{K_S}{\rightleftharpoons} S{\cdot}CD + Br_2 \xrightarrow{k_2^B} \text{products} \quad (17B)$$

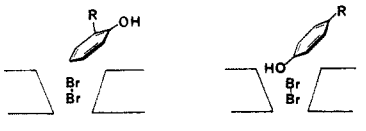
complex (eq 17B) (see also Scheme I). For these two models eq 14 is replaced by two equivalent equations:

$$k_2^* = k_2 + k_2^A[CD]/K_B \quad (18A)$$

$$k_2^* = k_2 + k_2^B[CD]/K_S \quad (18B)$$

Thus, the rate constants k_2^A and k_2^B, presented in Table II, can be obtained from values of k_3, knowing K_B and K_S.

Phenols. For phenols reacting via pathway A the values of k_2^A and k_2 parallel one another very closely and the ratios k_2^A/k_2, which measure the efficiency of catalysis, vary only between 3 and 31. Thus, for substrates with a 10^4 range of reactivity, the extent of catalysis is much the same. Furthermore, the rate ratios fall into two distinct groups. For phenol and 2-substituted phenols, which react mainly at para positions, the ratios are slightly higher (14–31) than those (3–8) for the 4-substituted phenols, which are constrained to react at an ortho position. This small difference in catalytic efficiency may indicate that it is easier for an unencumbered para position to approach the encapsulated bromine (**1**) than for an ortho position flanked by hydroxyl (**2**).

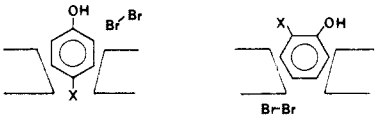


1 **2**

In any event, the difference in the amount of catalysis for 2- and 4-substituted phenols is small.[30] A plot of log k_2^A vs log k_2 (Figure 3) is reasonably linear (r = 0.9851) with a slope of 1.12 (sd = 0.07), which means that the catalyzed and uncatalyzed pathways are almost equally sensitive to the nature of the substituent on the phenol and have virtually the same Hammett ρ^+ values.[31] This close similarity is consistent with a relatively free molecule of the phenol in a largely aqueous environment (pathway A) reacting with a form of bromine which is slightly more reactive than is normal.

For reaction by pathway B the values of k_2^B are generally larger, with the rate ratios k_2^B/k_2 falling in the range 3–440 (Table II). However, within this range of values there are no clear trends or obvious groupings.[32] For unsubstituted phenol the ratio is 440, for 2-substituted phenols the ratios are 63–350, and for 4-substituted phenols the range is 3–300. Within each of these groups there are no apparent correlations between the ratios and the nature of the substituent. This is not what is expected for reaction between a complexed phenol and free Br_2 (pathway B, Scheme I); there should be a clearer distinction between the behavior of the 2- and 4-substituted derivatives.

For encapsulated 4-substituted phenols the hydroxyl group is in the bulk water and the ortho positions are situated above the lip of the CD cavity,[4,5c,d,18a] where they should be reasonably accessible for reaction with external bromine (**3**). In contrast,



3 **4**

the reactive para position of a 2-substituted phenol is probably embedded in the CD cavity[5d,33] and less accessible to an external reagent (**4**). Thus, for reaction via pathway B, the 4-substituted phenols should show more catalysis (larger k_2^B/k_2) than do the 2-substituted phenols. They do not.

Overall, the results for phenols are more consistent with pathway A (eq 17A and Scheme I). It appears that the interface of the CD cavity and the aqueous medium provides an environment that is only slightly different from the bulk medium but in which Br_2 is somewhat more reactive.

Phenoxide Ions. As found in other studies,[1-3] the values of k_2 for phenoxide ions (Table I) are virtually constant, consistent with reaction at diffusion-controlled rates.[24,34] Similarly, the rate constants k_3 for the CD-catalyzed reaction show very little variation (Table I). The largest k_3 is for 3-nitrophenoxide ion, and a possible reaction involving Br_3^- was considered; none was detected in the presence (or absence)[36] of CD. Likewise, no reaction between 4-nitrophenoxide ion and Br_3^- was found.

For reaction by pathway A the rate constants k_2^A fall in the narrow range of (1–6) × 10^{10} M^{-1} s^{-1} (Table II). This virtual constancy *strongly* suggests[24,37] that the reaction of phenoxide ions with the CD·Br_2 complex is diffusion controlled. The k_2^A values

(29) The third possibility of reaction within a ternary complex is considered later.

(30) A rate ratio of 20 (typical for para attack) corresponds to a difference in free energy of activation of 1.77 kcal/mol while a ratio of 5 (for ortho attack) is equivalent to a difference of only 0.95 kcal/mol.

(31) For seven 4-substituted phenols the ρ^+ value is −5.21 (r = 0.980).[3a]

(32) Compared to Figure 3, a plot of log k_2^B vs log k_2 shows more scatter (r = 0.9381, slope = 1.26, sd = 0.18).

(33) Tee, O. S.; Takasaki, B. K. *Can. J. Chem.* **1985**, *63*, 3540.

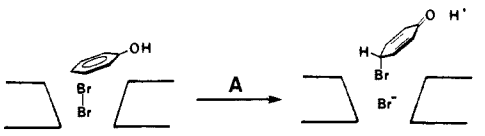
(34) Diffusion-controlled rate constants for bromine attack on simple enols are in the range (2–5) × 10^9 M^{-1} s^{-1}.[35] The rate constant for the reaction of Br_2 with Br^- is similar.[10]

(35) Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393. Tapuhi, E.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 5758. Guthrie, J. P.; Cossar, J.; Klym, A. *J. Am. Chem. Soc.* **1984**, *106*, 1351. Chiang, Y.; Kresge, A. J.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 6392. Keefe, J. R.; Kresge, A. J.; Toullec, J. *Can J. Chem.* **1986**, *64*, 1224.

(36) From data showing considerable scatter, Bell and Rawlinson[1] extracted a rate constant of 2.8 × 10^7 M^{-1} s^{-1} for the reaction of Br_3^- with 3-nitrophenoxide ion. Reaction with such a rate constant would not compete with bromine attack under the present conditions. In keeping with this, we have obtained data[3c] that show no significant reaction involving Br_3^- when $[Br^-] \leq 0.1$ M.

(37) (a) Caldin, E. F. *Fast Reactions in Solution*; Wiley: New York, 1964. (b) Amdur, I.; Hammes, G. G. *Chemical Kinetics: Principles and Selected Topics*; McGraw-Hill: New York, 1966; pp 59–64. (c) Moelwyn-Hughes, E. A. *The Chemical Statics and Kinetics of Solutions*; Academic Press: London, U.K., 1971; Chapter 5. (d) Jordan, P. C. *Chemical Kinetics and Transport*; Plenum Press: New York, 1979; Chapter 9, p 309ff.

Scheme II



are greater than is normal ($(2-8) \times 10^9$ M^{-1} s^{-1}) for the encounter of neutral species of similar size[24,34,35,37] but the encounter in question involves species of quite different sizes: a phenoxide ion and a large supermolecule,[38] CD·Br_2. According to the usual model of solute diffusion[24,37] based on the Smoluchowski equation and the Stokes–Einstein equation,[39] the encounter rate constant (k_{en}) is sensitive to the effective radii of the diffusing species such that the encounter of species of disparate sizes is predicted to be more likely.[40] Thus, interpretation of the results for phenoxide ions in terms of pathway A seems quite reasonable.

In contrast, the values of k_2^B for phenoxide ions do not appear plausible. They do not vary in any meaningful way with the substituent on the phenoxide ion (Table II), and three of them are unreasonably high ($>10^{11}$ M^{-1} s^{-1}), much greater than one can attribute to diffusion.[24,34,37,41]

We conclude, therefore, that the data for the CD-mediated bromination of phenoxide ions are more consistent with pathway A. The same conclusion was reached for phenol bromination (see above), but with quite different arguments.

Ternary Complex? The possibility of reaction of a ternary complex (S·CD·Br_2) was mooted earlier.[7] If such a process (eq 19) were to be involved, $k_3 = k_t/K_BK_t$. Evaluation of this model

$$S + CD + Br_2 \underset{K_B}{\rightleftharpoons} S + CD{\cdot}Br_2 \underset{K_t}{\rightleftharpoons} S{\cdot}CD{\cdot}Br_2 \xrightarrow{k_t} \text{products} \quad (19)$$

is difficult, as estimates of K_t are not available. However, the parallelism of k_3 and k_2 (Table I) suggests that K_t, if meaningful, does not vary greatly for different phenols. Further, in the bromination of the phenoxide ions the formation of the ternary complex would have to be rate limiting and diffusion controlled (see above).

On the basis of the present (and previous)[7] results there is no clear necessity to invoke reaction within discrete ternary complexes having lifetimes longer than a normal encounter.[24,37]

Origin of Catalysis. The data for both phenol and phenoxide ion bromination are best interpreted in terms of pathway A. In the case of the anions, the catalysis appears to originate in an elevated encounter rate (see above). However, for the reaction of phenols a higher encounter rate, per se, should not be important *unless* it is associated with a more favorable formation of the reactive encounter complex. Such is quite possible since the formation of the encounter complex (eq 20)[37b,d,43,44] is strongly dependent on the size of the species involved:

$$K_{en} = 4\pi N(r_A + r_B)^3/3000 \quad (20)$$

Thus, if Br_2 in the reactive encounter is replaced by the much larger CD·Br_2 supermolecule,[38] the formation constant K_{en} should be greatly increased. If this interpretation is correct, the question then becomes why should the rate of reaction within the {CD·Br_2/phenol} encounter be similar to that within the normal {Br_2/phenol} encounter?

Table III. Dissociation Constants for Complexes of α-Cyclodextrin with Phenols and Their Anions[a]

substituent	K_S, mM phenol	K_S, mM anion
H	50[b]	
2-Me	4.3[c]	
2-Br	52[d]	~110[e]
2-NO_2	38[d]	~40[e]
2,6-Me_2	15[c]	
3-NO_2	6.6[f]	4.2[g]
4-Me	83[b]	
4-*t*-Bu	7.0[c,h]	
4-Br	1.4[d]	1.2[d]
4-COOEt	4.8[c]	
4-CN	7.1[i]	1.6[i]
4-NO_2	4.4[d,j]	0.47[k]

[a] In H_2O, at 25 °C Values for the anions are only given where necessary. [b] Reference 6. [c] Estimated from the kinetic data (see Experimental Section). [d] Measured spectrophotometrically. [e] Approximate value (see Experimental Section). [f] Interpolated between values measured by Harata;[20] Eadie–Hoftsee analysis of our kinetic data gave 7.1 mM. [g] Calculated from measured thermodynamic parameters.[18a] [h] Bender et al.[18c] have K_s = 12 mM. [i] Reference 18a. [j] Several quite different values appear in the literature but the most reliable is probably 4.7 mM, as discussed by Gelb et al.[18b] [k] Reference 18b.

The answer probably resides in a differential "medium" effect since the reaction occurs at the interface of the aqueous medium and the cyclodextrin cavity. Bromine attack on a phenol produces two ions[45] so that the reaction rate increases sharply with the solvent ionizing power.[26] For example, from the values of k_2 in water (Table I) and acetic acid[26] the Grunwald–Winstein *m* value[46] is ~0.96, close to the values (~1.0) found for S_N1 solvolyses[47] and the bromination of alkenes.[48] Thus, water facilitates normal phenol bromination by stabilizing the incipient cation and anion.[45] For reaction within the encounter complex {CD·Br_2/phenol} water may also stabilize the incipient cation while binding to CD may provide the necessary assistance to the departure of Br^- (Scheme II). Such assistance is plausible since CD forms a complex with Br^-.[8] Moreover, formation of Br^- within the CD cavity would not require the extensive solvent reorganization which is a major contributor to the barrier of the normal reaction.[49]

One final point remains to be discussed: whereas CD modestly catalyzes the bromination of phenols and their anions (k_2^A/k_2 = 3–30), for anisole the catalysis is not quite as effective (k_2^A/k_2 ~ 0.5).[7] This difference, which is not large, may reflect a mechanistic difference between bromine attack on a phenol[45] (or phenoxide ion) and that on an anisole. With *p*-methylanisole no CD-mediated bromination was detected[7] and so k_2^A must be much smaller than k_2 (see footnote 10 in ref 7). Reasons why this should be so are not immediately apparent. Possibly anisole reacts via pathway B (with $k_2^B \sim k_2$)[7] and this pathway is blocked for *p*-methylanisole.[7]

The model for CD-catalyzed bromination of phenols presented above (Scheme II) is supported by studies[50] of the reverse type

(38) Lehn, J.-M. *Science (Washington, D.C.)* **1985**, *227*, 849.
(39) Edward, J. T. *J. Chem. Educ.* **1970**, *47*, 261.
(40) For example, if the effective radius of one of the diffusing species is 10 times that of the other, the value of k_{en} is about 3 times greater than that for species of the same size.
(41) The older literature, reviewed by Ridd,[24] has some rate constants of $>10^{11}$ M^{-1} s^{-1} for halogen attack on enols and enolates. They were based on estimates of enol content which are now considered unreliable.[42]
(42) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1.
(43) Reference 37c, Chapter 3.
(44) Roecker, L.; Meyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 746.
(45) In the conventional mechanism, bromine attack on phenol produces a protonated cyclohexadienone + Br^-.[3c] However, we have evidence that bromine attack is general base assisted,[3b,3e,13b] in which case the initial products would be H_3O^+, neutral cyclohexadienone,[3c,13] and Br^- (water being the general base).
(46) Leffler, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963; pp 297–300.
(47) Bentley, T. W.; Schleyer, P. von R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1. Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 5741.
(48) See Ruasse et al.[27]
(49) The reaction produces ions,[45] and even though this is much easier in water, it occurs at a price. A large contribution to the activation barrier must come from solvent reorganization around the incipient ions, particularly around the leaving bromide ion.[46,47] For recent views on solvation changes in ion-forming S_N2 solvolysis, see: Kurz, J. L.; Lee, J.; Love, M. E.; Rhodes, S. *J. Am. Chem. Soc.* **1986**, *108*, 2960.
(50) Bennett, J. M. M.Sc. Thesis, Concordia University, Montreal, Canada, 1986.

of reaction. These will be reported in detail shortly.[51]

Experimental Section

Materials. α-Cyclodextrin and the phenols were obtained from Aldrich. Old or discolored phenol samples were purified by distillation or recrystallization.

Bromine solutions were made up as previously described.[7] Stock solutions of the phenols (0.05–0.50 M) were prepared in HPLC grade methanol, and small volumes of these were diluted with the desired medium. Normally, $[phenol]_0 = 0.50$ mM and $[Br_2]_0 = 0.05$ mM after 1:1 mixing in the stopped-flow apparatus. In some cases, the concentrations were reduced by 5 to slow down the faster reactions.

For studies at pH 0–2 the media contained HCl and 0.1 M salt ([KBr] + [NaCl]). The pH values were calculated from [HCl] by using an activity correction based on the Davies' equation.[52] For pH > 2, buffers were prepared following Perrin[53] so that $I = 0.11$ M (buffer + [KBr] + [NaCl]).

Kinetic Methods. Rates were measured at 25.0 ± 0.1 °C by monitoring the disappearance of bromine near 265 nm (Br_3^- band)[9a] using a stopped-flow apparatus interfaced to a microcomputer.[9b] In cases where the decay of cyclohexadienones[3c,13] caused tailing infinity readings, the wavelength was set at 275 nm. In a few cases where tailing was still evident the infinity reading was obtained by the Swinbourne method.[54] One drive syringe of the stopped-flow apparatus contained phenol + medium + CD (0–10 mM) while the other contained Br_2 + medium but *no CD* since it slowly reacts with bromine.[7]

With a tenfold excess or more of substrate, bromine decrease exhibited good first-order behavior for more than 90% reaction. The derived first-order rate constants[9,13] were converted to k_2^{app} values in the normal way.[7]

Equilibrium Measurements. For the 2-bromo-, 4-bromo-, 2-nitro-, and 4-nitrophenols the dissociation constants of the CD–phenol complexes (K_S) were determined spectrophotometrically.[55] Solutions were made in 0.01 M HCl + 0.1 M NaCl ($I = 0.11$ M) and kept at 25 °C. Values of K_S obtained at several wavelengths were averaged.

When the spectral changes associated with complexation are very small and/or K_S is high, the spectrophotometric method is not usable.[18b] For several such cases K_S was obtained from the kinetic data by using an Eadie–Hofstee type of analysis,[4] as set out 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 8 and rearrangement lead to

$$k_2' = k_3K_S + K_S(k_2 - k_2')/[CD]$$

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].

Attempts to measure K_S values directly for the 2-bromo- and 2-nitrophenoxide ions were not successful and they were not accessible from the kinetic data. Therefore, we used the effect of CD on the ionization of the parent phenols to estimate K_S for these anions. As reported by Connors and Lipari[19] (and here confirmed), added CD does not alter the pK_a of 2-nitrophenol, implying that K_S for the 2-nitrophenoxide ion is essentially equal to that of its phenol (~40 mM). For 2-bromophenol, spectrophotometric determination[56] (five pHs, three wavelengths) gave $pK_a = 8.30$ in the absence of CD and 8.34 in the presence of 10 mM CD (25 °C, $I = 0.11$ M). These two pK_a's are related by the equation[57]

$$pK_a' = pK_a + \log \frac{K_s'(K_S + [CD])}{K_S(K_S' + [CD])}$$

where pK_a' is the apparent constant in the presence of CD, K_S is for the phenol·CD complex, and K_S' is for the anion·CD complex. From this expression and knowing pK_a, pK_a', K_S, and [CD], we estimate that $K_S' \sim 110$ mM for the 2-bromophenoxide ion.

The values of K_S used and their origins are collected in Table III.

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Supplementary Material Available: Tables of apparent second-order rate constants for the bromination of phenols and phenoxide ions as a function of various concentrations (Tables S1–S6) (7 pages). Ordering information is given on any current masthead page.

(51) Tee, O. S.; Bennett, J. M. *J. Am. Chem. Soc.*, submitted for publication.
(52) Guenther, W. B. *Chemical Equilibrium*; Plenum Press: New York, 1975; p 230.
(53) Perrin, D. D. *Aust. J. Chem.* **1963**, *16*, 572.
(54) Swinbourne, E. S. *Analysis of Kinetic Data*; Nelson: London, 1971; pp 78–84.
(55) Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
(56) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*, 3rd ed.; Chapman and Hall: London, 1984; Chapter 4.
(57) This is the logarithmic form of an equation derived by Connors and Lipari.[19] We have independently derived this form, assuming absorbance measurements are used.