Catalysis of the Debromination of 4-Alkyl-4-bromo-2,5-cyclohexadienones in Aqueous Solution by α-Cyclodextrin

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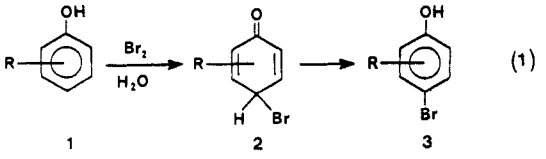
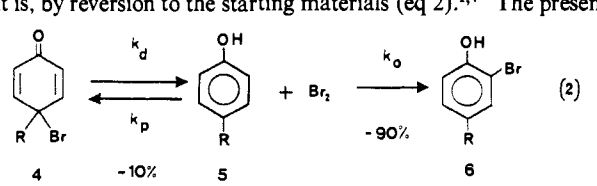
Abstract: α-Cyclodextrin (CD) has little or no effect on the rates of enolization of transient 4-bromo-2,5-cyclohexadienones (**2**), formed during the aqueous bromination of alkylphenols. In contrast, saturation kinetics and large catalytic effects are observed for the debromination of the title dienones (**4**), formed by ipso bromine attack on 4-alkylphenols (alkyl = Me, Et, *i*-Pr, *n*-Pr, *t*-Bu, 3,4-diMe). With the exception of the *n*-propyl case, the extent of the catalysis (k_c/k_u = 23–78) and the dissociation constants of the CD·dienone complexes (K_d = 2.32–4.83 mM) show surprisingly little variation for the different alkyl groups. The simplest interpretation of the results is that the CD-catalyzed debromination reaction involves attack by *free* bromide ion on the CD·dienone complex. However, the kinetically equivalent pathway, reaction between the *free* dienone **4** and the CD complex of bromide ion, is much more consistent with the low sensitivity of the catalysis to the length and size of the different alkyl groups. For this mechanism the rate enhancements are much larger (2400–4600) and almost constant. They imply that Br^- in its CD complex is a stronger nucleophile than bromide ion that is completely solvated by water. The preferred mechanism is the microscopic reverse of that postulated for the CD-catalyzed bromination of phenols. The common transition state for the ipso bromination of **5** (R = Me) and the debromination of **4** (R = Me) is strongly bound by CD ($K_d \sim 4.5 \times 10^{-5}$ M).

Labile 4-bromo-2,5-cyclohexadienones can be observed during the aqueous bromination of phenol and alkylphenols.[1-4] These intermediates decompose by two different reactions, depending on the position of the alkyl substituent. If the starting phenol **1** has a vacant para position, a transient dienone **2** is formed that enolizes to the 4-bromo product **3** (see eq 1).[1-3] On the other



1 2 3 (1)

hand, for *p*-alkylphenols about 10% of the initial bromine attack occurs ipso to the alkyl group, leading to an "*ipso*-dienone"[4,5] **4** that cannot enolize. Under the reaction conditions this species represents a "cul-de-sac" and so it decomposes by debromination, that is, by reversion to the starting materials (eq 2).[1,4] The present



4 ~10% 5 ~90% 6 (2)

paper reports studies of the effects of α-cyclodextrin[6] on the enolization of **2** and on the debromination of **4** in dilute aqueous acidic solution.

Cyclodextrins are oligosaccharides composed of six or more glucose units in a toroidal arrangement that gives rise to a hydrophobic cavity.[6] Both in solution and in the solid state, they form guest–host complexes in which the guest is encapsulated in the cavity of the cyclodextrin.[6,7] Consequently, cyclodextrins can have significant effects on the reactions of guest molecules. In many cases the effect is simply one of inhibition (which can be useful),[6,7a] but in other cases distinct catalytic effects are observed[6-8] and these effects can be quite dramatic when the cyclodextrin is functionalized and/or the substrate is carefully designed.[6,8]

Recently, we reported on the effects of α-cyclodextrin (CD) on the attack of bromine on phenols and on phenoxide ions.[9] This reaction, which leads to the formation of cyclohexadienones such as **2** and **4**, is catalyzed by CD.[9] It was a logical next step to find out if CD also affects the breakdown of these labile intermediates. We were particularly interested in the effect of CD on the debromination of the dienones **4**, since this reaction is the microscopic reverse of the ipso bromination of **5** (eq 2).

Results

We first investigated the effects of CD on the enolization of the transient dienones **2**,[1,2] formed during the bromination of four phenols in aqueous solution.[10] Disappointingly, we found only small variations in the rates (Table S1, Supplementary Material). For the most part, the rates increase slightly and then tail off at high [CD]. The largest increase (for the 2,6-dimethyl case) was only 13%, and most of the changes are on the order of the experimental error. In view of the very small rate variations with [CD], attempts to analyze the data were abandoned and no further experiments on **2** were carried out. In sharp contrast, we found that CD exhibits large catalytic effects on the debromination of the *ipso*-dienones, **4**.

Before presenting these results, it is necessary to provide additional background information. In aqueous solution, bromide ion and CD form a weak complex that has a dissociation constant K_1 = 0.286 M.[11] At the concentrations of Br^- used in our work, this formation results in an appreciable reduction in the amount of CD that is available for the complexation of other species; the available CD is given by

$$[CD] = [CD]_t K_1/(K_1 + [Br^-]) \quad (3)$$

where $[CD]_t$ is the total added CD. As in our earlier work,[9] the

(1) Tee, O.S.; Iyengar, N. R.; Paventi, M. *J. Org. Chem.* **1983**, *48*, 759.
(2) Tee, O. S.; Iyengar, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 455.
(3) Tee, O. S.; Iyengar, N. R. *Can. J. Chem.* **1987**, *65*, 1714.
(4) Tee, O. S.; Iyengar, N. R.; Bennett, J. M. *J. Org. Chem.* **1986**, *51*, 2585.
(5) Fischer, A.; Henderson, G. N. *Can. J. Chem.* **1979**, *57*, 552; **1983**, *61*, 1045.
(6) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978.
(7) (a) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (b) Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Eds. *Inclusion Compounds*; Academic: London, 1984; Vol. 2, Chapter 8; Vol. 3, Chapter 12.
(8) (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170; *Science (Washington, D.C.)* **1982**, *218*, 532. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. (c) Breslow, R.; Trainor, G.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739. (d) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146.
(9) (a) Tee, O. S.; Bennett, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 269. (b) We have also studied the effect of CD on anisole bromination. See: Tee, O. S.; Bennett, J. M. *Can. J. Chem.* **1984**, *62*, 1585.
(10) The substituents were none, 3-methyl, 2,5-dimethyl, and 2,6-dimethyl.
(11) Wojcik, J. F.; Rohrbach, R. P. *J. Phys. Chem.* **1975**, *79*, 2251. This reference was inadvertently left out of ref 9b.

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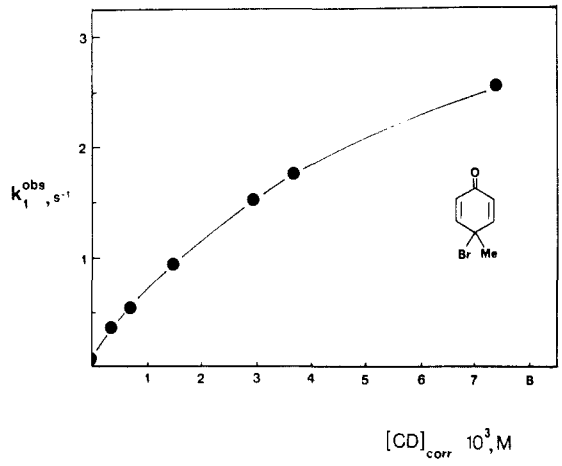


Figure 1. Dependence of the rate of debromination of the dienone **4** (R = Me) on the effective concentration of α-cyclodextrin in aqueous solution containing 0.1 M KBr, 0.05 M HCl, and 0.2 mM phenol (bromine trap) (data from Table S4). Note that the [CD] has been corrected for the complexation with Br^- (eq 3).

concentration of CD given by eq 3 was used in all data analysis.

The rates of decay of the dienone **4** (R = Me), generated in situ from 4-methylphenol and bromine,[1,4] increase with [CD] in a nonlinear manner (Table S2). Also, the rates at high [CD] vary in proportion to [Br^-] (Table S2) and [H^+] (Table S3), as found for the normal reaction.[4] Thus, CD significantly catalyzes the debromination of **4** (R = Me), the rate being about 18 times faster in the presence of 5 mM CD.

The data for **4** (R = Me) (and other dienones generated in situ) do not conform well to Michaelis–Menten kinetics,[6] as several rate constants and equilibria are involved. Therefore, a rigorous analysis of the k^{obsd} vs [CD] data (Table S2) was not attempted, as it would be extremely cumbersome and probably not convincing. The reason for this is that the debromination is not a simple process and the rate constant for the decomposition of **4** does not represent that of a unique, rate-limiting step.[1,4] As shown in eq 2, the debromination step (k_d) produces *p*-alkylphenol and bromine, which rapidly react again. The bromine, present in steady-state amounts,[4] is then partitioned between ortho and para attack (k_o and k_p) so that the overall rate constant (at constant [H^+] and [Br^-]) is given by

$$k^{obsd} = k_d k_o/(k_o + k_p) \qquad (4)$$

where the rate constant k_d contains [H^+][Br^-]. Thus, the effect of CD on k^{obsd} must be a composite of its separate effects on the steps represented by k_d, k_o, and k_p. Earlier work showed that the effect of CD on the bromination steps ($k_o + k_p$) is complex due to the presence of five equilibria[9a] but, in principle, an analysis of the data based on eq 4 could be worked out. However, it would be complicated and probably unreliable.[12]

To overcome this problem we developed a procedure in which the debromination of *preformed ipso*-dienones **4**[13] is carried out in the presence of an efficient trap for the liberated bromine.[14] With such a trap,[15] the bromination steps (**5** → **4** and **5** → **6**) are eliminated so that the debromination step (**4** → **5**) is solely rate limiting ($k^{obsd} = k_d$) and it can be studied separately.[4]

Figure 1 shows the dependence on [CD] of first-order rate constants for the decomposition of preformed **4** (R = Me) in aqueous HCl + KBr, with phenol as the bromine trap.[15] Similar behavior was obtained with other [Br^-] (Table S5) and other dienones **4** (Table S6, discussed later). The rate constants increase with [CD] and, in contrast to the initial experiments (see above), the increases conform well to Michaelis–Menten behavior.[6] Therefore, the data were analyzed by the Eadie–Hofstee approach[6,16] and for the data in Figure 1 the analysis yields K_d = 4.83 mM for the dissociation constant of the CD·dienone complex and k_c = 4.07 s^{-1} for the apparent rate constant for reaction of this complex. Thus, the magnitude of the catalysis at saturation, measured by the ratio k_c/k_u, is 78, where k_u is the rate constant at zero [CD].[17]

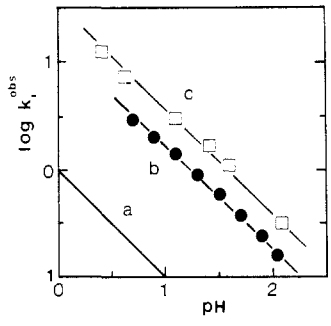


Figure 2. pH dependence of rate constants for the debromination of the dienone **4** (R = Me) in 0.1 M aqueous KBr: (a) the normal reaction (no CD, no bromine trap);[1,4] (b) in the presence of 5 mM CD; (c) in the presence of 5 mM CD *and* a bromine trap (an excess of phenol).

Table I. Constants for the Debromination of 4-Alkyl-4-bromo-2,5-cyclohexadienones (**4**) in the Presence of α-Cyclodextrin[a]

alkyl	K_d, mM	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u	k_c/K_d, M^{-1} s^{-1}
Me[b]	4.83	0.0520	4.07	78	840
Et	2.87	0.0591	2.32	39	810
i-Pr	2.43	0.0709	1.60	23	660
n-Pr	0.752	0.141	1.65	12	2200
t-Bu[b]	2.32	0.0433	1.20	28	520
3,4-diMe	3.55	0.175	5.15	29	1500

[a] At 25 °C, in 0.1 M KBr + 0.1 M HCl, and in the presence of excess phenol as a trap for bromine (see Experimental Section). The value "k_c/K_d" is the apparent second-order rate constant for the reaction of **4** with CD under the specified conditions. [b] In 0.1 M KBr + 0.05 M HCl.

The CD-catalyzed reaction is dependent on [Br^-][17b] and [H^+], as is the normal reaction in the absence of CD.[1,4] Figure 2 shows the pH dependence of rate constants for the debromination of the dienone **4** (R = Me) in the presence of a bromine trap and 5 mM CD (line c) (Table S4). Also shown there are the profiles for the normal reaction (line a)[1,4] and for reaction in 5 mM CD with *no* bromine trap (line b) (Table S3). Clearly, all three reactions are proton catalyzed and the relative rates (a:b:c) are 1:18:38.

Comparison of the data shown in Figure 2 (lines b and c) provides further, useful information. For the decomposition of **4** (R = Me) in the absence of the trap for bromine the rate constant k^{obsd} has the form in eq 4, whereas for reaction carried out with bromine trapping, $k^{obsd} = k_d$ (see above). Thus, from the ratio of the rate constants measured under the two different conditions we can estimate the fraction of ortho bromine attack: $k_o/(k_o + k_p)$.[4]

The rate constant for proton catalysis of the decomposition of **4** (R = Me) in the presence of phenol as the bromine trap (in 0.1 M KBr and 5 mM CD) is 38 M^{-1} s^{-1} (Figure 2c and Table S4) whereas with no bromine trap the value is 18 M^{-1} s^{-1} (Figure 2b

(12) Since the data treatment would require the use of various constants from different origins[9a] and some approximations.

(13) The dienones **4** were preformed from the appropriate phenol **5** and bromine in a weak buffer of pH 4.5, *in the absence of added bromide ion.* Since the decay of **4** depends on [H^+][Br^-], they are long-lived enough under these conditions to allow the trapping experiments (see Experimental Section) to be carried out.[4]

(14) This approach was specifically devised for the present work. However, it was also used profitably in studies of the buffer catalysis of the debromination of **4** (R = Me).[4]

(15) After various trials, phenol was found to be a suitable trap for bromine (see footnote 21 of ref 4).

(16) The Eadie–Hofstee approach is statistically superior to the more traditional Lineweaver–Burk treatment. See: Dowd, J. E.; Riggs, D. S. *J. Biol. Chem.* **1965**, *249*, 863.

(17) (a) Analysis of the data obtained at other [Br^-] produced comparable results, but k_c varies with [Br^-] (Table S5). (b) In 5 mM CD values of k^{obsd} (=0.955, 1.20, 1.86 s^{-1}) vary in direct proportion to [Br^-] (=0.050, 0.075, 0.100 M) (Table S5).

Table II. Constants Evaluated for the Two Reaction Models A (Eq 5) and B (Eq 7) for the CD-Catalyzed Debromination of the Dienones **4**[a]

		model A (eq 5)		model B (eq 7)	
alkyl	k_u'	k_c^A	k_c^A/k_u'	k_c^B	k_c^B/k_u'
Me	1.04	81	78	4800	4600
Et	0.591	23	39	2300	3900
i-Pr	0.709	16	23	1900	2700
n-Pr	1.41	17	12	6500	4600
t-Bu	0.866	24	28	3000	3500
3,4-diMe	1.75	52	29	4200	2400

[a] At 25 °C, normalized to 0.1 M HCl. The rate constants (in M^{-1} s^{-1}) are as follows: k_u' for the reaction of **4** with bromide ion, k_c^A for the reaction of the CD complex of **4** with bromide ion (eq 5), and k_c^B for the reaction of the CD complex of bromide ion with **4** (eq 7).

and Table S3). From the ratio of these two rate constants the fraction of ortho attack is 0.47 (in 5 mM CD); this is about half the value found earlier for the normal reaction (0.92).[4] Thus, CD promotes the para (ipso) attack of bromine on *p*-methylphenol much more than it does ortho attack.

This conclusion is consistent with the absorbance changes ($A_0 - A_\infty$) observed during decay of the dienone **4** (R = Me) that had been generated in the presence of CD (Table S2). The changes, which are indicative of the amount of **4** (R = Me)[18] formed during the fast, initial reaction of bromine with *p*-methylphenol,[4] increase with [CD] and level off at ~2.5 times the value in the absence of CD.[19] They are also consistent with CD catalysis favoring para bromine attack relative to ortho attack.

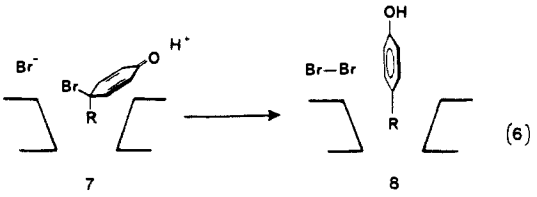
We have measured the rates of decomposition of five other *ipso*-dienones **4** in solutions of varying [CD], containing the trap for bromine (Table S6). In all cases there are significant rate increases, and the data give satisfactory Eadie–Hofstee plots. The deduced constants for all six dienones are collected in Table I. The most notable feature of these constants is that they do not vary markedly for the different alkyl groups. This is clearly seen with the dissociation constants (K_d = 0.75–4.8 mM), the catalytic ratios (k_c/k_u = 12–78), and the apparent second-order rate constants (k_c/K_d = 520–2200 M^{-1} s^{-1}), which measure the "specificity" of the CD catalysis.

Discussion

The decompositions of the *ipso*-dienones **4** in the presence of α-cyclodextrin *and* a trap for bromine exhibit Michaelis–Menten behavior (e.g., Figure 1), and the simplest interpretation of the results, designated model A, is that the catalysis is due to the reaction of *free* bromide ion with the CD complex of the dienone, **4** (eq 5). Rate constants (k_c^A) for this model are collected in

$$Br^- + CD + 4 \underset{K_d}{\rightleftharpoons} Br^- + CD\cdot 4 \xrightarrow{k_c^A} \text{products} \qquad (5)$$

Table II. The most likely arrangement from which this reaction could take place would be with the alkyl group R of the dienone inside the CD cavity and the ipso bromine outside, accessible for attack by external bromide ion (see **7**, eq 6).



(6)

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For model A the extent of catalysis (k_c^A/k_u') varies only from 12 to 78 (Table II). This seems quite unreasonable, given the variability in the alkyl group R, in respect of both chain length and steric bulk. In particular, for R = Et, *i*-Pr, and *t*-Bu and for the 3,4-dimethyl compound, the ratio is virtually constant (39, 23, 28, and 29, respectively). With these differently sized groups, the dienones **4** should sit progressively higher in the CD cavity[20] so that nucleophilic attack by external bromide ion on the ipso bromine at C-4 should become easier.

Similarly, the "specificity" of the catalysis, as measured by the apparent third-order rate constants, k_c^A/K_d, is very low: the values range only between 6600 and 23 000 M^{-2} s^{-1}.[21] Again, if the reaction took place as shown in eq 6, one would expect to observe greater sensitivity to the alkyl substituent inside the CD cavity.

The dissociation constants of the CD·dienone complexes also do not vary greatly. For R = Me, Et, *i*-Pr, *t*-Bu, and 3,4-diMe, the values of K_d = 4.8, 2.9, 2.4, 2.3, and 3.5 mM, respectively. This lack of variability makes little sense if the binding of the dienones **4** to α-cyclodextrin involves the insertion of the alkyl group R into the CD cavity (see **7**). The binding constants of alcohols, alkylphenols, and alkylphenyl acetates, for example, all show a much wider variation with the length and size of the alkyl group.[20] However, the near constancy of K_d for the dienones **4** *is* reasonable if it is the ipso bromine that enters the CD cavity (see **9**). This orientation is not unreasonable since bromine bound

9 10

to carbon is quite lipophilic.[20] In keeping with this, we note that CD binds *p*-bromophenol 59 times more strongly than *p*-methylphenol and 5–9 times more strongly than *p-tert*-butylphenol.[9a]

A possible exception to the mode of binding shown in **9** is with the *n*-propyl derivative, **4** (R = *n*-Pr), for which the complex with CD is appreciably stronger (K_d = 0.75 mM). This dienone may represent the sole case of binding through the alkyl group (**7**) because the extended *n*-propyl chain is better able to occupy the cyclodextrin cavity (see **10**).

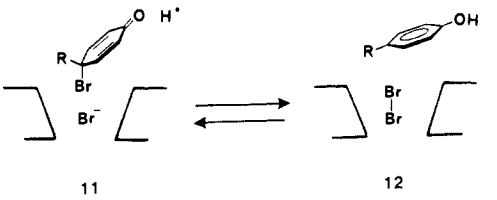
In the above discussion two other possible modes of binding have been ignored. The mode in which the dienone **4** binds with its carbonyl group in the CD cavity is considered unlikely since the carbonyl is the most hydrophilic part of **4** and so it is more likely that it projects into the aqueous medium, outside the hydrophobic CD cavity.[20] Also, the simultaneous binding of the ipso bromine *and* the alkyl group of the dienone in the CD cavity has been rejected. Space-filling (CPK) models, which have been extremely useful in rationalizing results and in designing novel systems,[6,8] clearly indicate that there is insufficient space for the binding of both groups in the CD cavity.

We believe that our kinetic results are more easily interpreted in terms of reaction between *free* dienone **4** and the CD complex of bromide ion (eq 7 and Scheme I). This pathway, which we

$$CD + Br^- + 4 \underset{K_1}{\rightleftharpoons} CD\cdot Br^- + 4 \xrightarrow{k_c^B} \text{products} \qquad (7)$$

designate as model B, is kinetically equivalent to that shown in

Scheme I



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(18) The exact amount cannot be adduced since the necessary extinction coefficients are not accurately known under the reaction conditions. Likewise, quantitative analysis of the absorbance changes vs [CD] is not feasible since there are several species in solution that form complexes with CD.[9]

(19) The absorbance changes for the decomposition of preformed **4** (R = Me) in the presence of the bromine trap vary only slightly with [CD].

(20) Matsui, Y.; Nishioka, T.; Fujita, T. *Top. Curr. Chem.* **1985**, *128*, 61.

(21) The highest value is for the *n*-propyl case, which may well be exceptional (see later). Otherwise, the largest value is that for the methyl derivative (17000 M^{-2} s^{-1}).

eq 5 and so the apparent third-order rate constants (k_c^A/K_d), evaluated for model A, can be equated with k_c^B/K_I; the resulting values of k_c^B are presented in Table II.

The extents of catalysis, as shown by the ratios k_c^B/k_u', are large, ranging from 2400 to 4600 (Table II). More significant, however, is that the ratios are so very similar (less than a twofold range) for substituents of varying length (1–4 carbons) and size (Me to *t*-Bu). Further, the ratio for the 3,4-dimethyl dienone is barely different from those for the monosubstituted derivatives. These observations are entirely consistent with a transition state in which the alkyl group of the dienone **4** is outside of (and away from) the cyclodextrin cavity so that its size and shape are of little consequence (**11**, Scheme I). This arrangement can, of course, be most easily attained from the encounter of the free dienone with the CD complex of bromide ion (eq 7).

The proposed pathway for the CD-catalyzed debromination of **4** (**11** → **12**, Scheme I) is also compatible with the conclusions resulting from our earlier studies of the CD-mediated bromination of phenols.[9a] Largely on the basis of substituent effects, we argued that the CD-catalyzed process involves reaction between free phenol and the CD·bromine complex (**11** ← **12**, Scheme I). Thus, as required by the principle of microscopic reversibility,[22] the proposed transition states for bromination and debromination are identical.

From comparison of the rate constants for the debromination of **4** (R = Me) in the presence and absence of a bromine trap (Figure 2b,c) it was concluded that CD catalyzes para bromine attack on *p*-methylphenol more than ortho attack. Absorbance values for **4** (R = Me) formed in the presence of CD support the same conclusion (see Results). This finding can be quantified, as follows. For the normal reaction of bromine with *p*-methylphenol $k_o = 5.7 \times 10^5$ M^{-1} s^{-1} and $k_p = 5.0 \times 10^4$ M^{-1} s^{-1}.[4] For reaction with the CD·Br_2 complex $k_2 = 5.0 \times 10^6$ M^{-1} s^{-1}.[9a] Assuming the fraction of ortho attack is 0.47 (see Results), $k_o = 2.35 \times 10^6$ M^{-1} s^{-1} and $k_p = 2.65 \times 10^6$ M^{-1} s^{-1}. Thus, k_o is enhanced by a factor of 4.1 whereas k_p is elevated by 53. These values are quite consistent with the earlier studies of phenol bromination where it was found that CD catalysis of para bromine attack on ortho-substituted phenols is greater than that of ortho attack on para-substituted phenols.[9a]

Previously,[4] we estimated that the equilibrium constant for the ipso attack of bromine on *p*-methylphenol (eq 8, R = Me) is *K*

$$\mathbf{5} + Br_2 \overset{K}{\rightleftharpoons} \mathbf{4} + H^+ + Br^- \quad (8)$$

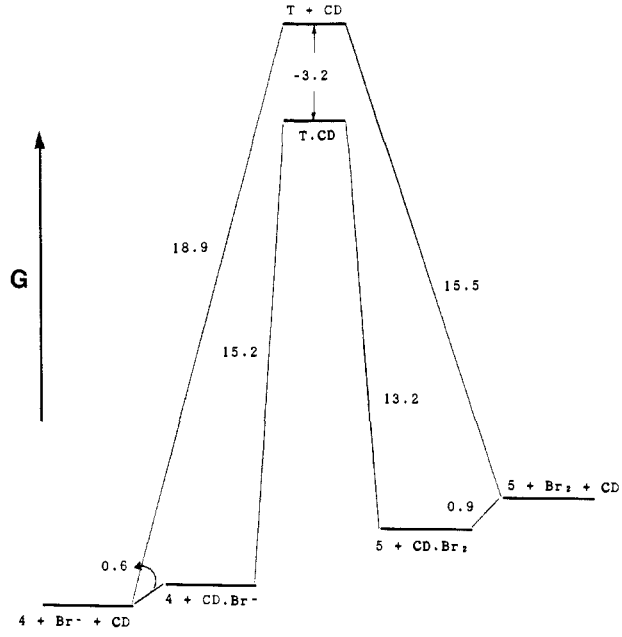
$$\mathbf{5} + CD{\cdot}Br_2 \overset{K'}{\rightleftharpoons} \mathbf{4} + H^+ + CD{\cdot}Br^- \quad (9)$$

$= [\mathbf{4}][H^+][Br^-]/[\mathbf{5}][Br_2] = 5600$ M. In like manner, we now estimate that the analogous constant for the ipso reaction of **5** (R = Me) with the CD complex of bromine (eq 9) is $K' = 56$ M.[23] The factor of a 100 difference between *K* and *K'* is perfectly reasonable since CD binds bromine[24] about 100 times more strongly than Br^-.[11]

Alternatively, the equilibrium constant for the reaction of the CD·**5** (R = Me) complex with bromine is $K'' = 1.3 \times 10^5$ M,[25] about 23 times larger than *K*. Again, the difference is reasonable since CD binds the dienone **4** (R = Me) about 20 times more strongly than it does **5** (R = Me).[24] These estimations of *K'* and *K''* show that the results of our studies of CD-catalyzed bromination[9a] and of debromination (this work) are compatible, regardless of the mechanistic interpretation (model A (eq 5) or model B (eq 7)).

We can also estimate the effect of CD on the energy of the transition state for the debromination of **4** (R = Me) (and the ipso bromination of **5** (R = Me)). For the debromination of **4** (R = Me) by H^+ and Br^- alone, trapping experiments in dilute HCl gave[4] a rate constant of 8.9 M^{-2} s^{-1}, while for the same reaction in 10 mM CD the value is 1680 M^{-2} s^{-1},[26] a rate ratio that corresponds to a stabilization of the transition state by 3.11 kcal/mol.

Chart I. Relative Gibbs Energies (kcal/mol) of the Pathways for Bromide Ion Induced Debromination of the Dienone **4** (R = Me) and the Reverse, Ipso Bromination of **5** (R = Me) Catalyzed (Scheme I) and Uncatalyzed by α-Cyclodextrin (CD)[a]



[a] Evaluated for [**5**] = 0.5 mM (≫[Br_2]), [CD] = 10 mM, and [Br^-] = [H^+] = 0.1 M. Note the stabilization of the transition state (T) by ~3.2 kcal/mol due to binding with CD.

The same quantity may also be estimated from bromination data. For the ipso (para) bromination of **5** (R = Me)[4] $k_p = 5.0 \times 10^4$ M^{-1} s^{-1}, whereas in 10 mM CD $k_p = 2.37 \times 10^9 \times 0.53 \times 0.010 = 1.25 \times 10^7$ M^{-1} s^{-1},[27] which is equivalent to an energy difference of 3.27 kcal/mol. These two estimates are in reasonable agreement, given that they were arrived at entirely *independently* and each depends on various quantities of different origins.

The relative Gibbs energies of the species involved in the uncatalyzed and CD-catalyzed processes, under realistic reaction conditions, are shown in Chart I. This diagram shows clearly that the dominant factor in the catalysis by CD (in either direction) is the lowering of the transition-state energy. A value of ~3.2 kcal/mol for the energy of stabilization (in 10 mM CD) implies strong binding of CD in the transition state between **11** and **12**, with a $K_d \sim 4.5 \times 10^{-5}$ M, much stronger than the binding of CD to either Br^- or Br_2 (K_d = 0.286 M and 2.1 mM, respectively). Thus, as is now well recognized with enzymes,[28] the efficacy of the catalyst is determined much more by its ability to bind to the reaction transition state than to the reactants.

We now consider the possible origin of the catalysis shown by α-cyclodextrin in the debromination of the *ipso*-dienones (**4**). Assuming that the catalyzed pathway involves reaction between free dienone **4** and the CD·Br^- complex (eq 7 and Scheme I), the catalytic ratios ($k_c^B/k_u' = 2400$–4600) imply that Br^- in its CD complex is a stronger nucleophile than bromide ion as it normally exists in aqueous solution. This is not unreasonable since it is now well established that poorly solvated anions are, in general, more

(22) For a recent, rigorous discussion, see: Laidler, K. J. *Chemical Kinetics*, 3rd ed.; Harper and Row: New York, 1987; pp 129–131.

(23) Based on $k_2 = 5.0 \times 10^6$ M^{-1} s^{-1} for the reaction of CD·Br_2 with **5** (R = Me),[9a] 53% para (ipso) attack (see Results), and $k_c^B = 4800$ M^{-1} s^{-1} in 0.1 M HCl (Table II).

(24) Breslow, R.; Campbell, P. *Bioorg. Chem.* **1971**, *1*, 140.

(25) Based on $k_2 = 2.0 \times 10^8$ M^{-1} s^{-1} for the reaction of bromine with CD·**5** (R = Me),[9a] 53% para (ipso) attack (see Results), and $k_c^A = 81$ M^{-1} s^{-1} in 0.1 M HCl (Table II).

(26) Derived from the second-order rate constant for the reaction of 4 (R = Me) with CD ($k_c/K_d = 840$ M^{-1} s^{-1}, Table I) in 0.1 M KBr and 0.05 M HCl.

(27) Based on $k_3 = 2.37 \times 10^9$ M^{-2} s^{-1} (see Table I of ref 9a) and 53% para attack (see Results) in 0.01 M CD.

(28) Fehrst, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman: New York, 1985; Chapter 12. Lienhard, G. E. *Science* (*Washington, D.C.*) **1973**, *180*, 149.

nucleophilic.[29-32] Thus, nucleophilic reactions of anions in aprotic solvents[29,30] (or the gas phase)[31,32] proceed much more rapidly than in hydroxylic solvents.[33] For example, the attack of Br^- on methyl iodide is 16 000 times faster in DMF than it is in methanol, and this rate enhancement is almost solely due to the free energy of transfer of Br^- from MeOH to DMF.[29a,30]

In the normal reaction of bromide ion with **4** (and a proton) a significant part of the activation barrier must arise from desolvation of the nucleophile and solvent reorganization.[30,32-36,38] On the other hand, for attack by the CD·Br^- complex much of this desolvation has already been achieved during the formation of the complex. Thus, instead of attack by a bromide ion that is strongly solvated by and surrounded by several water molecules,[40] debromination can occur with a bromide ion that is partially enclosed by a CD molecule (Scheme I) and only weakly solvated.[41] Also, as progress is made along the reaction coordinate, binding of the bromine molecule being formed in the CD cavity must become increasingly important.

In view of the fact that α-cyclodextrin strongly catalyzes the debromination of the *ipso*-dienones **4**, it is surprising that it has such small effects on the enolization of the transient dienones **2** (eq 1). The small rate increases and decreases that are observed with increasing [CD] (Table S1) indicate that (at least) two equilibria are involved. Thus, it may well be that the catalytic effects on one process are largely canceled by the inhibitory effects on others. We suggest that CD catalyzes the enolization (**2** → **3**) but that it is offset by strong catalysis of the debromination (**1** ← **2**, eq 10).[42] Since the effect of CD on the rebromination

$$\mathbf{1} + Br_2 \rightleftarrows H^+ + Br^- + \mathbf{2} \rightarrow \mathbf{3} \qquad (10)$$

(**1** → **2**) is complicated by the presence of several equilibria,[9a] the overall effect of CD on the flux of **2** to **3** would then be a complex composite of many effects.

Conclusions

Studies of the effect of α-cyclodextrin on the bromination of phenols[9a] and on the debromination of **4** (this work) lead to a consistent picture of the CD-catalyzed reactions. The common transition state for bromination and debromination has the two bromine atoms inside the CD cavity while the organic moiety and its substituents are outside, in a largely aqueous environment (Scheme I). As a result, the substituent effects for the catalyzed and the uncatalyzed reactions in either direction are closely similar. Binding of the common transition state to CD is relatively strong, with $K_d \sim 4.5 \times 10^{-5}$ M.

Bromide ion complexed by CD appears to be a stronger nucleophile than normally hydrated Br^-.

Experimental Section

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

Bromine solutions were made up by weight, as previously described.[9] Substrate (a phenol) solutions were made by dilutions of stock solutions (0.1 or 0.5 M), made up in HPLC-grade methanol. Stock CD solutions (0.1 M) in the desired medium were used within 24 h of preparation.

The acidic aqueous media contained HCl and 0.1 M salt ([KBr] + [NaCl]). The pH values were calculated from [HCl] using an activity correction based on the Davies' equation.[43]

Trapping Experiments. For debromination of the *ipso*-dienones **4** in the presence of a bromine trap,[15] the following procedure was used. Solutions (0.4 mM) of the appropriate *p*-alkylphenol **5** and of bromine were prepared in a weak acetate buffer of pH ~4.5 that contained *no added bromide ion*. Aliquots (5 mL) of each of these solutions in syringes were simultaneously squirted into a small beaker to generate a solution of the dienone **4** (~0.02 mM).[44] This solution was then placed in the stopped-flow apparatus and mixed with a solution of phenol (0.4 mM) containing twice the desired [KBr] and [HCl]. Therefore, immediately after the mixing in the stopped-flow apparatus, [**4**] and [phenol] were ~0.01 and 0.2 mM, respectively. The ~20-fold excess of phenol ensures the rapid consumption of liberated bromine, as discussed in the main text.

For experiments with no bromine trap (Tables S1–S3), the dienones (**2** or **4**) were generated in situ from the appropriate phenol (**1** or **5**) (0.5 mM) and bromine (0.05 mM).[1,4]

Kinetic Methods. Rates were measured at 25.0 ± 0.1 °C by monitoring the decay of the dienone (**2** or **4**) at 240–250 nm,[1,2,4] using a stopped-flow apparatus interfaced to a microcomputer.[4,45] First-order rate constants (k^{obsd}) were obtained by analysis of absorbance traces covering about 90% reaction. In a few cases where the infinity readings drifted, they were estimated by the Swinbourne method.[46]

For the analysis of k^{obsd} vs [CD] saturation curves, where [CD] was taken from eq 3, an Eadie–Hofstee approach[6,16] was used. Such analyses afforded the constants k_c and K_d, given in Table I.

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Registry No. **4** (R = Me), 84559-80-8; **4** (R = Et), 102260-53-7; **4** R = Pr-*i*), 102260-55-9; **4** (R = Pr-*n*), 102260-54-8; **4** (R = Bu-*t*), 102260-56-0; **4** (3,4-diMe), 102260-57-1; α-cyclodextrin, 10016-20-3.

Supplementary Material Available: Tables of first-order rate constants for the decay of the dienones **2** and **4** as a function of various concentrations (Tables S1–S6) (5 pages). Ordering information is given on any current masthead page.

(29) For recent summaries, see: (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; Chapter 4. (b) Klumpp, G. W. *Reactivity in Organic Chemistry*; Wiley: New York, 1982; pp 186–203. (c) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 316ff.

(30) Parker, A. J. *Adv. Phys. Org. Chem.* **1967**, *5*, 173; *Chem. Rev.* **1969**, *69*, 1.

(31) In the gas phase the "activity" of a naked anion can be so great that nucleophilic displacement has no enthalpic barrier and the rate of reaction is controlled by entropy. See: Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219. Caldwell, G.; Magnera, T. F.; Kebarle, P. *J. Am. Chem. Soc.* **1984**, *106*, 959. Riveros, J. M.; Josĕ, S. M.; Takashima, K. *Adv. Phys. Org. Chem.* **1985**, *21*, 197.

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(34) Ritchie, C. D. In *Solute–Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1976; Vol. 2, p 229.

(35) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373. Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239.

(36) Solvent reorganization is also of importance in solvolytic S_N2 displacements of methyl derivatives[37,38] and in the attack of oxygen anion bases on carbon acids.[39]

(37) Kurz, J. L.; Kurz, L. C. *Isr. J. Chem.* **1985**, *26*, 339. Kurz, J. L.; Lee, J.; Love, M. E.; Rhodes, S. *J. Am. Chem. Soc.* **1986**, *108*, 2960.

(38) Others argue that solvation reorganization is not of primary importance in the S_N2 reactions of methyl derivatives. See: Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87.

(39) Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420. Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969.

(40) The heat of hydration of Br^- is 78 kcal/mol: Blandamer, M. J. *Adv. Phys. Org. Chem.* **1977**, *14*, 204.

(41) It will be interesting to see if the nucleophilicity of Br^- is enhanced in other reactions.

(42) The formation of **2** from **1** is irreversible under the normal reaction conditions (pH 0–4, [Br^-] ~ 0.1 M).[1,2] This means that in the absence of CD the debromination of **2** does not compete effectively with its enolization.

(43) Guenther, W. B. *Chemical Equilibrium*; Plenum: New York, 1975; p 230.

(44) Since only ~10% of bromine attack is ipso.[4]

(45) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.

(46) Swinbourne, E. S. *Analysis of Kinetic Data*; Nelson: London, 1971; pp 78–84.