Catalysis of Electrophilic Bromine Attack by α-Cyclodextrin

Oswald S. Tee * and Bushra C. Javed
Department of Chemistry and Biochemistry, Concordia University, Montréal, Québec, Canada H3G 1M8

The aqueous bromination of various aromatic and heteroaromatic substrates is catalysed by α-cyclodextrin (α-CD), and the oxidation of formic acid (by bromine attack on formate ion) is similarly catalysed. The kinetic results are interpreted in terms of reaction between *free* substrate and the α-CD·Br_2 complex, which is slightly more reactive than free bromine. This interpretation is consistent with the finding that substituent effects for the catalysed and uncatalysed reactions are essentially identical and that the transition state stabilization afforded by α-CD varies little for substrates having a 10^{10} range of reactivity.

Cyclodextrins (CDs) are water-soluble, cyclic oligomers of glucose that form guest–host complexes with a wide range of organic and inorganic species in aqueous solution.[1,2] As a result of such complexations, CDs can influence the course of chemical reactions by acting as inhibitors or catalysts.[1-3] Inhibitory effects may have various practical applications,[3] but it is largely as potential catalysts that cyclodextrins and their derivatives have attracted the attention of physical organic chemists.[1,4] Likewise, our interest in CDs stems from their ability to affect reactivity[1,5] and to exhibit supramolecular behaviour.[6]

One way in which CDs may influence reactions is by providing a microenvironment, the CD cavity, that is less polar than the bulk aqueous medium.[1] For example, the accelerating effect of β-CD on the decarboxylation of activated carboxylate anions in aqueous solution is similar to that of organic co-solvents.[1,5,7] Significant effects can be anticipated for other reactions showing sensitivity to solvent polarity.[8]

Heterolytic processes of neutral substrates usually show strong solvent dependence due to the differential stabilization of the reactants, the ionic intermediates and their associated dipolar transition states.[8] Such is the case for the electrophilic addition of bromine to alkenes[9] and for the bromination of phenol,[10] both of which have Grunwald–Winstein *m* values near 1.0, meaning that these reactions are very much slower in apolar media than in water. Thus, one might reasonably expect that bromination in aqueous solution would be retarded or even inhibited by CDs for two reasons: (i) the formation of complexes with the CD which lowers the concentrations of the free reactants in solution; (ii) slower reaction within the microenvironment of the less polar CD cavity.

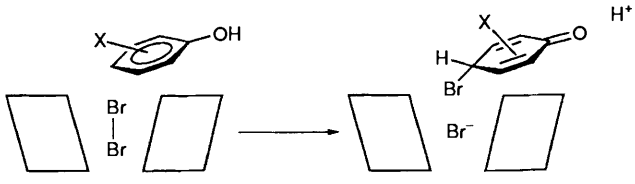
In contrast to these expectations, previous work showed that the brominations of anisole[11] and of phenols[10] are not strongly retarded by α-CD,[1] indicating that some form of catalysis by the CD occurs. For phenols that bind weakly to α-CD, actual rate increases are observed in spite of the various complexations that reduce free reactant concentrations. Also, the reaction kinetics clearly indicate a termolecular transition state containing the substrate, bromine, and *one* molecule of α-CD. From the effects of substituents on the reaction kinetics it was concluded that the catalysis by α-CD most likely results from reaction of CD-bound bromine with free substrate [eqn. (1a)] and that the α-CD·Br_2 complex is 3–31 times more reactive than free Br_2 towards phenols and phenoxide ions. For the kinetically equivalent reaction of the substrate·CD complex with free bromine [eqn. (1b)], the rate constants (k_2^B) for phenols do not correlate sensibly with the nature and position of the substituent, and for three of the phenoxide ions the values of k_2^B would be unreasonably large ($> 10^{11}$ dm^3 mol^{-1} s^{-1}).

$$S + CD + Br_2 \underset{K_B}{\rightleftharpoons} S + CD{\cdot}Br_2 \xrightarrow{k_2^A} \text{products} + CD \quad (1a)$$

$$S + CD + Br_2 \underset{K_S}{\rightleftharpoons} S{\cdot}CD + Br_2 \xrightarrow{k_2^B} \text{products} + CD \quad (1b)$$

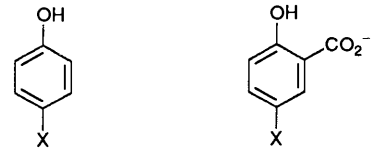
Additional support for the reaction sequence in eqn. (1a) was obtained from studies[12] of the debromination of 4-alkyl-4-bromocyclohexa-2,5-dienones (so-called '*ipso*-dienones'[13]). This reaction, which is the microscopic reverse of *ipso* bromination, showed strong catalysis by α-CD and the *in*sensitivity of the catalysis to different alkyl substituents on the *ipso*-dienone was taken to mean that the dienone is outside the CD cavity during the catalysed reaction.

So, for phenols it was proposed that the catalysed bromination ensues from a configuration in which the bromine is inside the α-CD cavity while the substrate is outside and in a largely aqueous environment (Scheme 1).[10] In the reverse direction, catalysed debromination occurs by attack of α-CD-bound bromide ion on the dienone, with acid catalysis (Scheme 1).[12]



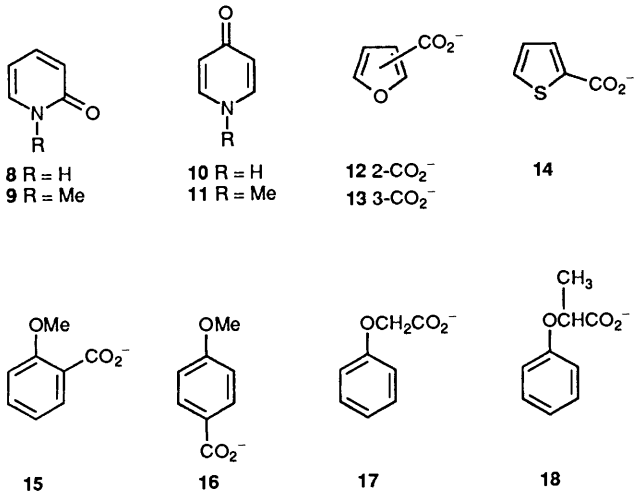
Scheme 1

The present paper reports further studies on the ability of α-CD to catalyse electrophilic bromine attack, using a broader range of substrates (**1–18**, formic acid, and formate ion). The object of the work was to probe the generality of the catalytic effect since we were concerned that it might be peculiar to the phenols. Mainly, we have used other aromatic and hetero-



1 X = F
2 X = Cl
3 X = Br
4 X = I

5 X = Br
6 X = SO_3^-
7 X = NO_2



aromatic substrates, the bromination of most of which had been studied earlier in other contexts.[14]

Some results concerning the effect of α-CD on the oxidation of formic acid by bromine have already been published.[15] Early communication was prompted by a report of similar results but with a significantly different interpretation.[16]

Results and Discussion

Several of the species in the reacting solutions are involved in complexation equilibria. We begin by reviewing these equilibria and how we take account of them.[10,11]

Equilibria.—For various reasons we carry out bromination in aqueous solution in the presence of an excess of bromide ion,[17] following the consumption of bromine through the decrease in the strong absorbance due to tribromide ion, which is formed from bromine and bromide ion in a fast equilibrium. (2).[18]

$$Br_3^- \rightleftharpoons Br_2 + Br^-; \qquad K = 0.0562 \text{ mol dm}^{-3} \quad (2)$$

When Br^- is in large excess the fraction of free Br_2 is given by eqn. (3).

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

However, α-CD forms complexes with all three bromine species[11,19,20] [eqns. (4)–(6)].

$$CD{\cdot}Br_3^- \rightleftharpoons CD + Br_3^-; \qquad K_T = 0.17 \text{ mmol dm}^{-3} \quad (4)$$

$$CD{\cdot}Br_2 \rightleftharpoons CD + Br_2; \qquad K_B = 2.1 \text{ mmol dm}^{-3} \quad (5)$$

$$CD{\cdot}Br^- \rightleftharpoons CD + Br^-; \qquad K_I = 0.286 \text{ mol dm}^{-3} \quad (6)$$

Although the complexation of Br^- is weak[20] it cannot be neglected because $[Br^-]$ is high (= 0.1 mol dm^{-3}) and it reduces the concentration of free α-CD below that introduced (=$[CD]_0$) [eqn. (7)]. For the purposes of data analysis this

$$[CD] = [CD]_0K_I/(K_I + [Br^-]) \quad (7)$$

corrected quantity must be used.

In the presence of Br^- and α-CD the combined effect of the above equilibria is to reduce the fraction of free bromine further, in accordance with eqn. (8).

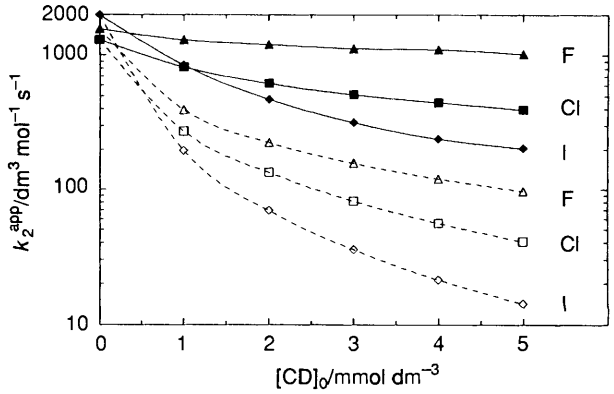


Fig. 1 The effect of α-cyclodextrin on rate constants for the bromination of *p*-fluoro-, *p*-chloro- and *p*-iodo-phenol (in 0.1 mol dm^{-3} KBr and 0.1 mol dm^{-3} HCl, pH ≈ 1): filled symbols = observed data; open symbols = calculated points. The vertical scale is logarithmic to emphasize the difference between the observed and calculated values; the latter were obtained from eqn. (12), which assumes *no* α-CD-catalysed bromination.

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

The complexation of bromine[19] is quite strong but that of Br_3^- is 10 times stronger[11,15] and under the reaction conditions its effect is dominant (since $K_B[Br^-] > KK_T$). Our disagreement[15] with the conclusions of Han *et al.*[16] arose because they did not allow for the complexation of Br_3^- by α-CD [eqn. (4)].

Generally speaking, the substrate (S) also forms a complex with α-CD so that the fraction of free S is also reduced, eqn. (9).

$$f_S = [S]/[S]_0 = K_S/(K_S + [CD]) \quad (9)$$

In deriving eqns. (8) and (9) it is assumed that $[CD] \gg [Br_2]$ and $[S]_0$, respectively, which was the case in all our experiments.

Kinetics.—In the absence of α-CD, the brominations studied are second order[10,14,15] [eqn. (10)]. However, owing to the

$$S + Br_2 \xrightarrow{k_2} \text{products} \quad (10)$$

formation of Br_3^- from Br_2 the apparent second-order rate constants are attenuated by the factor f_B given in eqn. (3), according to eqn. (11). When $[Br^-] = 0.1$ mol dm^{-3}, as is the

$$k_2^{app} = k_2f_B \quad (11)$$

case throughout the present work, $f_B = 0.360$.

In the presence of α-CD, k_2^{app} is further reduced owing to the equilibria discussed above and it has the form given in eqn. (12),

$$k_2^{app} = k_2f_Sf_B \quad (12)$$

where f_S is taken from eqn. (9) and f_B is now given by the complex expression in eqn. (8). In the absence of other processes eqn. (12) should account for the variation of k_2^{app} with [CD] (and $[Br^-]$).[10,11,15] The fraction f_B decreases from 0.360 at zero [CD] to 0.0231 when $[CD]_0 = 5$ mmol dm^{-3}. Thus, if no other processes intervene, k_2^{app} *should decrease by at least a factor of* 16. If K_S is small, so that f_S is significantly less than 1, then k_2^{app} should decrease even further.

Table 1 shows the second-order rate constants for 20 different brominations, as a function of $[CD]_0$. In no case is k_2^{app} reduced by as much as a factor of 16. Fig. 1 shows the data for three *p*-halophenols and, as seen there, the three curves calculated on

Table 1 Second-order rate constants for bromination in the presence of α-cyclodextrin[a]

Substrate	k_2^{app}/dm^3 mol^{-1} s^{-1} at [CD]$_0$/mmol dm^{-3} =					
	0	1.0	2.0	3.0	4.0	5.0
1	1 560	1 300	1 200	1 120	1 100	1 020
2	1 300	818	620	513	449	396
4	1 990	844	473	318	240	204
5	54 500	54 000	43 700	42 500	39 200	34 900
6	39 500	24 600	19 900	18 700	18 000	16 500
7	5 790	2 750	1 990	1 710	1 510	1 410
8	6 490	2 820	2 080	1 760	1 610	1 560
9	12 400	3 670	2 220	1 620	1 300	1 120
10	3 270	1 630	1 290	1 080	1 020	997
11	3 420	1 190	760	558	451	389
12	8 330	3 130	1 970	1 610	1 450	1 330
13	18 800	8 730	6 240	5 240	4 730	4 530
14	484	179	106	76.4	65.3	55.5
15	5 620	2 180	1 380	978	800	689
16	10 600	3 620	2 240	1 630	1 300	1 140
17	1 960	696	418	351	242	209
18	66.3	27.8	17.8	12.3	9.53	8.71
HCOOH[b]	0.339	0.429	0.428	0.430	0.466	0.451
$HCOO^-$	11.4	15.7	16.0	15.4	15.7	15.8

[a] At 25 °C, [KBr] = 0.1 mol dm^{-3}. For the phenols (**1**, **2**, **4**) pH ≈ 1 (0.1 mol dm^{-3}HCl); for the pyridones (**8**–**11**) and all the carboxylate ions (**5**–**7**, **12**–**18**), including formate, pH = 5.0 (acetate buffer). *p*-Bromophenol (**3**) has been studied previously.[10] [b] At pH 2 (0.01 mol dm^{-3} HCl).

Table 2 Constants for the catalysis of the attack of bromine by α-cyclodextrin[a]

Substrate	k_2/dm^3 mol^{-1} s^{-1}	k_3/dm^6 mol^{-2} s^{-1}	K_S/mmol dm^{-3}	K_{TS}/mmol dm^{-3}
4-Fluorophenol	4350	1.1×10^7	120	0.40
4-Chlorophenol	3600	8.4×10^6	3.6	0.43
4-Bromophenol[b]	3900	8.5×10^6	1.4	0.46
4-Iodophenol	5500	1.9×10^7	0.47	0.29
5-Bromosalicylate	1.5×10^5	7.3×10^8	4.7	0.21
5-Sulfonatosalicylate	1.1×10^5	1.8×10^8	37	0.61
5-Nitrosalicylate	1.6×10^4	2.4×10^7	4.7	0.67
2-Pyridone	1.8×10^4	1.9×10^7	9.7	0.95
N-Methyl-2-pyridone	3.45×10^4	2.8×10^7	1.9	1.2
4-Pyridone	9100	1.3×10^7	9.9	0.70
N-Methyl-4-pyridone	9500	1.5×10^7	1.2	0.63
Furan-2-COO^-	2.3×10^4	2.1×10^7	4.4	1.1
Furan-3-COO^-	5.2×10^4	7.3×10^7	5.0	0.71
Thiophene-2-COO^-	1350	4.5×10^6	0.52	0.30
2-$MeOC_6H_4COO^-$	5500	1.2×10^7	0.87	0.46
4-$MeOC_6H_4COO^-$	180	8.5×10^5	0.45	0.21
$PhOCH_2COO^-$	1.6×10^4	4.7×10^7	0.66	0.34
$PhO(CH_3)CHCOO^-$	3.0×10^4	5.8×10^7	0.90	0.52
HCOOH[c,d]	0.94	5100	250[d]	0.18
$HCOO^-$[e]	32	1.75×10^5	high[f]	0.18

[a] At 25 °C. The origins of the K_S values are discussed in the text. [b] Original data from Tee and Bennett.[10] [c] Reacting *via* the anion, at pH 2.1. [d] Binds weakly to α-CD[16,24] and so this binding was ignored.[15,16] [e] At pH 5.0. [f] Apparently does not bind to α-CD at all.[24]

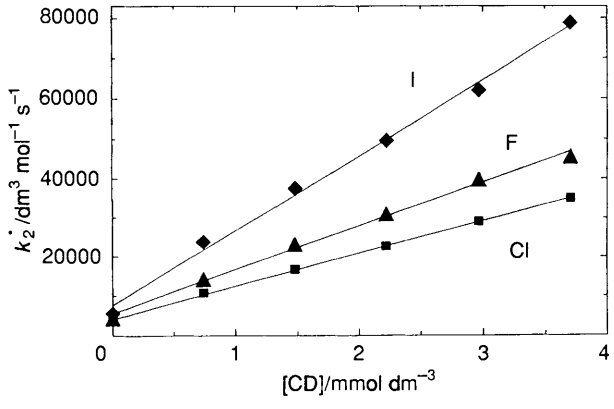


Fig. 2 Data for the same *p*-halophenols as in Fig. 1, linearized according to eqn. (15). Note that [CD] has been corrected for binding to Br^- using eqn. (7). The slopes of these plots give the catalytic coefficients (k_3) in Table 2.

the basis of eqn. (12) seriously overestimate the rate decreases due to added α-CD. Clearly, in every case in Table 1 there is another bromination process which increases k_2^{app} above that predicted by eqn. (12) and this we ascribe to catalysis by α-CD,[10] eqn. (13).

$$S + Br_2 + CD \xrightarrow{k_3} \text{products} + CD \qquad (13)$$

With respect to the processes discussed in the introduction, the third-order rate constant $k_3 = k_2^A/K_B$ or k_2^B/K_S, depending on whether one considers the reaction to proceed through the pathway in eqn. (1a) or that in eqn. (1b). The presence of the CD-catalysed process means that eqn. (12) must be expanded to eqn. (14) which can account for the observed data, but for

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

analytical purposes it is more convenient to rearrange it to a linear form,[10] eqn. (15). This linearization amounts to

$$k_2^* = (k_2^{app}/f_S f_B = k_2 + k_3[CD] \quad (15)$$

correcting k_2^{app} for the various equilibria involving the substrate and bromine. Fig. 2 shows that the procedure works well for the raw data plotted in Fig. 1. Data for the other substrates were also analysed using eqn. (15) or by direct non-linear fitting of eqn. (14), as detailed later. Values of k_2, obtained from measurements at zero [CD], and k_3 are collected in Table 2. If required, the rate constants for the processes in eqns. (1a) and (1b) can be calculated from $k_2^A = k_3 K_B$ and $k_2^B = k_3 K_S$, respectively (see above).

Substrates.—We first consider the behaviour of the four *p*-halophenols (**1–4**), of which the *p*-bromo derivative has been studied previously.[10] Because of the different 'sizes' of the F, Cl, Br and I substituents these substrates have a wide range of ability to bind to α-CD (K_S = 123–0.468 mmol dm^{-3})[21] but they should have similar reactivities towards bromine, judging by the Hammett σ_m constants of halogen substituents.[22] Therefore, the *p*-halophenols were chosen as probes of the importance, or otherwise, of the substrate's ability to bind to α-CD in the catalysed bromination reaction; in other words, to provide additional evidence as to whether the reaction proceeds as in eqn. (1a) or (1b).

As expected the substrates **1–4** have similar values of k_2 ($\approx$ 4000 dm^3 mol^{-1} s^{-1}) for normal bromination (Table 2) but they also have very similar rate constants ($k_3 \approx 10^7$ dm^6 mol^{-2} s^{-1}) for the CD-catalysed process, even though their K_S values vary over a 600-fold range. Thus, the catalytic efficiency (expressed as k_2^A/k_2 = 5–7) is quite insensitive to the ability of the halophenol to bind to α-CD, implying that binding of the substrate moiety is unimportant in the transition state and consistent with the portrayal of the reaction in Scheme 1.

The attack of bromine on phenols is subject to general-base catalysis,[14f] and in some cases transient cyclohexadienone intermediates are observable.[14e] These features might be contributing (or complicating) factors in the catalysis by α-CD and so we have studied other substrates where this is unlikely to be the case.

Salicylate ions (*e.g.*, **5–7**) show enhanced reactivity towards bromine, compared with phenols, which has been attributed to intramolecular proton transfer assisting electrophilic attack.[14c] Bromination of **5**, **6** and **7** also shows catalysis by α-CD, with k_2^A/k_2 = 3–10.* The bromination of pyridones[14a] does not show general-base catalysis,[14f] nor have 'long-lived' transients been observed. Nevertheless, bromine attack on both 2- and 4-pyridone and their *N*-methyl derivatives (**8–11**) shows mild catalysis by α-CD (k_2^A/k_2 = 2–3), slightly less than that shown by most phenols.[10] Furan and simple derivatives react readily with aqueous bromine, some giving electrophilic substitution whereas others give an oxidative addition.[14d] To avoid solubility problems, we have studied the effect of α-CD on the bromination of the furan-2- and furan-3-carboxylate ions (**12** and **13**), and of the related thiophene-2-carboxylate ion (**14**). All three derivatives show catalysis: k_2^A/k_2 = 2, 3 and 7, respectively.

Our initial study of the effect of α-CD on aromatic bromination involved anisole (methoxybenzene) and *p*-methylanisole as substrates.[11] At the time we concluded that the bromination of *p*-methylanisole is simply inhibited, in accord with eqn. (12), whereas the reaction of anisole showed some catalysis. For reaction *via* pathway (1a) the α-CD·Br_2 complex would be about half as reactive as free bromine (k_2^A/k_2 = 0.5); alternatively, for reaction *via* pathway (1b) the CD-bound anisole would be slightly less reactive than free anisole. Discrimination between the two kinetically equivalent pathways was not possible and the 'negative' result with *p*-methylanisole was of no help. We now view these conclusions with scepticism because of a lack of confidence in the values of K_S (3.7 mmol dm^{-3} for anisole and 15 mmol dm^{-3} for *p*-methylanisole)[20] used for the analysis of the kinetic data and we were unable to confirm these values owing to the low solubility of both derivatives in water. Lower K_S values, particularly for the *p*-methyl derivative, would mean there was more catalysed bromination than was surmised earlier[11] and so bring these anisoles more into line with the other substrates.

To avoid such problems, we sought anisole derivatives with greater solubility and chose four carboxylate anion derivatives: the *o*- and *p*-anisate anions (**15** and **16**), whose bromination had been studied earlier,[14b,c] and two phenoxyacetate derivatives (**17** and **18**). The latter two have reactivities (Table 2) towards bromine very similar to that of anisole (k_2 = 36 000 dm^3 mol^{-1} s^{-1}).[11] In the presence of α-CD all four anions show catalysis (k_2^A/k_2 = 5–10), similar to that for phenols.

Finally, as an example of a reaction involving bromine which is very different from electrophilic aromatic substitution, we studied the oxidation of formic acid.[15] This reaction, which involves electrophilic attack on the formate anion [eqn. (16)],[23] is catalysed by α-CD (k_2^A/k_{2u} = 12), as already reported by us[15] and by others.[16] Moreover, the catalytic efficiency observed at pH 2, where HCOOH is the dominant form in solution, and at pH 5, where $HCOO^-$ dominates, is exactly the same. In either case, it is highly unlikely that the CD-catalysed reaction proceeds as in eqn. (1b) because formic acid binds only weakly to α-CD (K_S = 250 mmol dm^{-3}) and formate ion not all, apparently.[16,24] Thus, it is virtually certain that the catalysis by α-CD takes place as in eqn. (1a).

$$Br_2 + HCO_2^- \longrightarrow 2\,Br^- + H^+ + CO_2 \quad (16)$$

Overall, the present substrates show behaviour that is similar to that found earlier for phenols, and so the catalytic effect of α-CD on bromine attack appears to be general.

Transition-state Stabilization.—In much of our recent work[5,25] we have used an approach due to Kurz[26] whereby one estimates apparent equilibrium constants (K_{TS}) for the dissociation of a catalyst from the transition state of the catalysed reaction. This approach, which is based on simple transition-state theory, has been used by enzymologists[27] and we have shown how it can be used for reactions mediated by cyclodextrins,[5,25] and other catalysts.[5b] Other authors have used the approach for metal-ion catalysis.[28]

For CD-catalysed bromination the value of K_{TS} is calculated from the ratio of the second-order rate constant for the normal reaction, eqn. (10), and the third-order rate constant for the CD-catalysed reaction, eqn. (13),[5,27b] [eqn. (17)] where TS

$$K_{TS} = [TS][CD]/[TS{\cdot}CD] = k_2/k_3 \quad (17)$$

and TS·CD are the transition states corresponding to k_2 and k_3, respectively.† This approach has been applied to the data for the α-CD catalysed bromination of phenols and phenoxide ions.[5] For these substrates values of K_{TS} vary only from 0.07 to 0.8 mmol dm^3, with most being between 0.1 and 0.5 mmol dm^{-3}. Thus, there is very similar transition-state stabilization for 15 substrates covering a range of reactivity of 4 × 10^7. Also, K_{TS} shows no clear correlation with K_S, which varies widely, implying no great similarity between substrate binding and transition-state binding. The lack of similarity is taken as

* Note that the α-CD-catalysed debromination of a related *ipso*-cyclohexadienone has also been studied.[5,12b]

† Recall that $k_3 = k_2^A/K_B$ or k_2^B/K_S if the reaction proceeds as in eqn. (1a) or (1b), respectively.

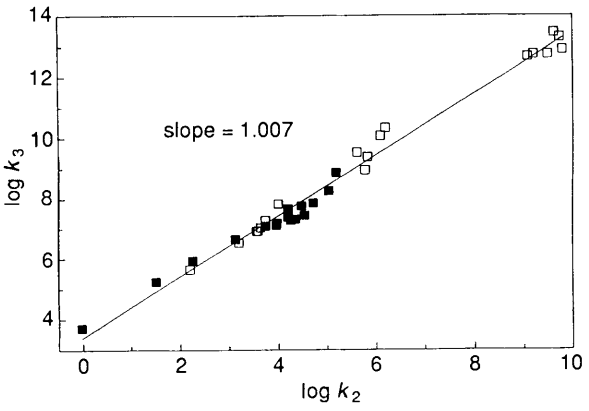


Fig. 3 Linear free energy relationship for the rate constants of α-cyclodextrin-catalysed and uncatalysed bromination. The slope of the correlation line is 1.007 ± 0.021 (r = 0.9926 for all 34 points). The filled squares are for the substrates in Table 2; the open symbols are for the phenols and phenoxide ions of a previous study.[10]

evidence that the transition state for the catalysed process is one in which the phenolic moiety is *outside* the CD cavity while the bromine is inside (Scheme 1).[5]

For the debromination of *ipso*-dienones[12] values of K_{TS} (defined appropriately) span a narrow range and are insensitive to the substituents on the dienone.[5] If the *ipso*-dienone was bound inside the cavity of α-CD in the transition state, particularly through its 4-alkyl group, one would expect there to be more of a dependence of K_{TS} on the substituents. Thus, the kinetic parameters for CD-catalysed debromination also suggest a transition state in which the organic moiety is outside the CD cavity and the two bromines atoms involved are inside (Scheme 1).

Values of K_{TS} for the substrates of the present study are given in Table 2. They show relatively little variation (0.18–1.2 mmol dm^{-3}) for substrates with a 10^5 range of reactivity towards bromine, and they seem to have no relationship with K_S values (*vide infra*). The four halophenols show remarkably similar transition-state stabilization (K_{TS} = 0.40, 0.43, 0.46, 0.29 mmol dm^{-3}), whereas they have very different abilities to bind to α-CD (K_S = 120, 3.6, 1.4, 0.47 mmol dm^{-3}) (Table 2). This finding implies that substrate binding and transition-state binding are very different with respect to the phenol moiety. It is inconsistent with inclusion of the phenol by α-CD during the catalysed bromination and so it affords more support for the mechanism in Scheme 1.

The α-CD catalysed brominations of the other aromatic and heteroaromatic substrates in the present study have K_{TS} values similar to those for phenols, as does the oxidation of formic acid at two different pHs (Table 2). This similarity indicates a comparable degree of transition-state stabilization for all of these substrates, suggestive of a common origin for the catalysis.

Combining the present results (Table 2) with the earlier ones[10] there is a good correlation of $\log k_3$ with $\log k_2$, covering 10 orders of magnitude and *with unit slope*, as shown in Fig. 3. This linear free-energy relationship is a direct consequence of the near constancy of K_{TS} for all the substrates, since $\log k_3 = \log k_2 + pK_{TS}$ [from eqn. (17)]. Also, because $k_3 = k_2^A/K_B$, $\log k_2^A$ correlates equally strongly with $\log k_2$ and with unit slope, as observed previously for the phenols.[10] This observation means that both the catalysed and uncatalysed bromination have the same effective Hammett ρ value, *i.e.*, the two reactions have exactly the same sensitivity to electronic variations in the substrates. At the same time, there is *no correlation* between the extent of the catalysis and the ability of the substrate to bind to α-CD: a plot of pK_{TS} and pK_S has a slope of −0.07 ± 0.07 and

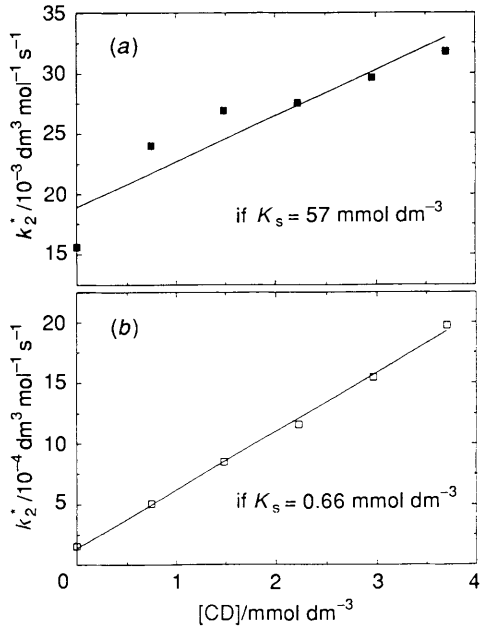


Fig. 4 Data for the phenoxyacetate ion (**17**), plotted according to eqn. (15): (*a*) for K_S = 57 mmol dm^{-3}, estimated from inhibition kinetics, the least-squares line has r = 0.9254; (*b*) with K_S = 0.66 mmol dm^{-3}, estimated by fitting, the line has r = 0.9987. Non-linear fitting of eqn. (14) to the k_2^{app} *vs.* [CD] data (Table 1), with f_S having the form in eqn. (9), gave the parameters: k_2 = (1.56 ± 0.01) × 10^4 dm^3 mol^{-1} s^{-1}; k_3 = (4.71 ± 0.74) × 10^7 dm^6 mol^{-2} s^{-1}; K_S = 0.66 ± 0.12 mmol dm^{-3}; and r = 0.9999.

r = 0.1673, implying that transition-state binding and substrate binding are quite unrelated.

Substrate Binding: a Caveat.—Analysis of the bromination rate data using eqn. (15) requires values of K_S for the calculation of f_S through eqn. (9). This presented no problem for the halophenols since values were already available.[10,21] For most of the other substrates we tried to use the inhibition of basic ester cleavage by α-CD to estimate K_S (see the Experimental section), with varying degrees of success. Values were obtained for the 5-bromo- and 5-sulfonatosalicylate ions (**5** and **6**) which led to good fits of eqn. (15). The method was not usable for the 5-nitrosalicylate ion (**7**) because it undergoes a second ionization[29] at the high pH of the inhibition experiment. Consequently, a fitted value of K_S was employed for **7** and for the pyridones (**8**–**11**), two of which also ionize in base.[14a]

A curious problem was encountered with the other aromatic and heteroaromatic carboxylate ions (**12**–**18**). From inhibition kinetics K_S values of 30–110 mmol dm^{-3} (Table 3) were estimated and these appear reasonable when compared with those of other aromatic carboxylate ions.[1,24,25] These values are sufficiently high (≫5 mmol dm^{-3}) that they should barely influence the bromination kinetics observed at low [CD] (< 5 mmol dm^{-3}, Table 1). The values for the furoate ions (**12** and **13**) lead to tolerable analyses using eqn. (15) but those for the remaining derivatives (**14**–**18**) do not! The *worst* example is shown in Fig. 4; the others show qualitatively similar, but less severe, deviations from linearity, suggesting a common origin to the behaviour. It is as though the K_S values deduced from inhibition kinetics are far too high since fitted values are much lower (Table 3). While this is possible, since inhibition is not always as total as expected,[25b] we suspect another origin. The fitted values of K_S are very low and probably too low for carboxylate ions (which generally bind fairly weakly to CDs).[1,24,25]

We speculate that the low fitted K_S values arise due to the formation of ternary complexes, formed from the aromatics,

Table 3 Apparent dissociation constants of complexes between α-CD and the aromatic carboxylate ions **12–18**[a]

Substrate	K_S/mmol dm^{-3} From inhibition[b]	Fitted[c]
12	57	4.4
13	74	5.0
14	62	0.52
15	109	0.87
16	32	0.45
17	57	0.66
18	65	0.90

[a] At 25 °C, in aqueous solution. [b] Obtained from the inhibitory effects of the anions on the basic cleavage of *m*-nitrophenyl acetate by α-CD. [c] From non-linear fitting of eqn. (14), with f_S having the form in eqn. (9).

bromine and α-CD. These 1 : 1 : 1 complexes could be stabilized by a charge-transfer interaction between the electron-rich aromatic and bromine,[30] as well as by the binding of bromine in the α-CD cavity.[11,15,19] Such complexes, which may be involved with anisoles also,[11] could have the appropriate geometry for reaction according to eqn. (1a), and akin to that shown in Scheme 1. Unfortunately, direct proof of the existence of highly reactive ternary complexes in the reacting solutions may be difficult and require considerable effort.[31]

In compiling the data in Table 2 we have used fitted values of K_S for **12–18** which lead to excellent adherence to eqns. (14) and (15) [*e.g.*, Fig. 4(*b*)], and to K_{TS} values very close to those of the other substrates. If, instead, we use the higher K_S values from inhibition studies (Table 3) then lower estimates of k_3 result from the 'slopes' of curvilinear plots of k_2^{app} against [CD] [*e.g.*, Fig. 4(*a*)] and K_{TS} values are 2–10 times higher (Table 3). Obviously lower k_3 values fall below the LFER correlation line in Fig. 3, but as a group they define a second correlation line, parallel to the first and with a slope near 1.0. Thus, even with the lower catalytic coefficients the same general trend in reactivity is observed.

In summary, we believe the abnormalities seen for **14–18** (and to a lesser extent **12** and **13**) result from the formation of ternary complexes which are not easily accounted for in our treatment of the data. Regardless, the general finding of catalysis of bromination by α-CD still stands and the magnitude of the catalytic effect seems to be fairly independent of the substrate structure.

Conclusions

On the basis of the above results, in particular the relative insensitivity of K_{TS} values and catalytic efficiencies to the structure and reactivity of different substrates, we conclude that the nature of the catalysis of bromine attack is much the same for all 34 substrates (Fig. 3), with only very minor variations in the magnitude of the catalysis for the different structural types. We find this remarkable since it means that the amount of transition state stabilization provided by α-CD is virtually constant for substrates with a 10^{10} range of reactivity. We take it as further support of the mechanism expressed in eqn. (1a) and that illustrated for phenols in Scheme 1. Ternary complexes with some charge-transfer character may be involved.

As discussed previously,[5,10] the catalysis of bromination and debromination by α-CD probably results from altered solvation of the reactants but it cannot be a simple microsolvent effect since bromine attack is much slower in media less polar than water. We suggest that it is an interfacial phenomenon, arising from the differential nature of the environment in which the catalysed reaction takes place: the aqueous exterior, where the organic moiety is largely situated, and the less polar CD cavity containing the two bromine atoms (Scheme 1). In the forward direction (bromination), solvent reorganization around the developing Br^- is less necessary than in normal aqueous solution since the ion is being formed in the CD cavity.[10] Conversely, for debromination, nucleophilic attack occurs by a partially desolvated bromide ion which therefore behaves as a stronger nucleophile.[12]

Experimental

The substrates used were available from previous studies[14,15] or were obtained from commercial suppliers. The solid samples were recrystallized before use. α-Cyclodextrin was obtained from Aldrich and used as received. The kinetic methods, stopped-flow apparatus and data acquisition were the same as in the previously reported studies.[10,11,15]

As discussed in the main text, inhibition kinetics were used to try to determine K_S values for many of the substrates. This method, which is described in detail elsewhere,[25b,32] depends on the binding of a compound (an 'inhibitor') to the CD to slow down a reaction accelerated by the CD. The method will only work properly if the inhibitor and the reaction employ the same site on the CD.[25b] In the present case we used the cleavage of *m*-nitrophenyl acetate by α-CD in a basic aqueous phosphate buffer of 11.6, a reaction that has been extensively studied and used in our laboratory.[25]

For those substrates where K_S was not available by other means, a value was obtained, along with k_3, by direct non-linear fitting of eqn. (14) with explicit inclusion of the term $K_S/(K_S + [CD])$ for f_S [eqn. (9)]. Non-linear regression analysis was carried out using in-house computer software, based on the Marquardt algorithm.[33]

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