# Multiple Pathways in the α-Cyclodextrin Catalysed Reaction of Iodide and Substituted Perbenzoic Acids

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The kinetic rate equation for the title reaction in aqueous acetate buffer has both first-order and second-order terms with respect to cyclodextrin concentration, due to catalysis both by one and by two molecules of cyclodextrin. The stabilisation of the transition state of the iodide–peracid reaction by cyclodextrin is examined using the pseudoequilibrium constant approach of Tee, *Carbohydr. Res.*, 1989, **192**, 181. This approach indicates that, depending on the nature of the peracid, the predominant pathway catalysed by one cyclodextrin molecule involves the reaction of either free iodide and a cyclodextrin–peracid complex or free peracid and a cyclodextrin–iodide complex. The latter two pathways are kinetically indistinguishable, but the corresponding terms in the rate equation are separated using the extrakinetic assumption of a Brönsted-type relationship. This assumption is reasonable since the uncatalysed reaction and that catalysed by two molecules of cyclodextrin show Brönsted-type relationships. The mechanism of catalysis is discussed in terms of the effect of cyclodextrin on the nucleophilicity of the iodide and acid catalysis *via* the protonation of the benzoate leaving group.

Inclusion of molecules or ions by cyclodextrin sometimes accelerates and sometimes inhibits their reactions, compared to the rates in the bulk aqueous medium. Steric effects are particularly important in fixing the reactant in a favourable or unfavourable configuration or conformation.[1] Also important for those reactions which are influenced by the relative permittivity of the reaction medium are microsolvent effects, derived from the relatively apolar properties of the interior of the cyclodextrin cavity.[1] It should be borne in mind, however, that the two lone pairs of each of the six or more bridging α-(1,4)oxygens in cyclodextrins are located in the middle of the cavity and lend the cyclodextrin some Lewis-base character.[2] Moreover, the cyclodextrin molecule is dipolar, α-cyclodextrin has six hydroxy groups at the narrower face of the cavity and twelve hydroxy groups at the wider face and a permanent dipole moment of 13.5 D has been calculated for the molecule.[3]

Most of the reactions mediated by cyclodextrin that have been studied are those involving either a covalent interaction between the host and the guest reactant or unimolecular decompositions or rearrangements of the guest.[1,2] Inhibition of bimolecular reactions by cyclodextrin due to separation of the reactants, is, however, very well known,[1,2] and indeed forms the basis of many of the practical applications of cyclodextrins as stabilisers.[4] Recently, a number of detailed mechanistic studies of the effects of cyclodextrins on bimolecular reactions in solution have appeared in the literature. Macartney has shown that the rate of outer sphere oxidation of 4-*tert*-butyl catechol by transition metals decreases substantially upon inclusion of the reductant by cyclodextrin, owing to steric hindrances to effective donor–acceptor orbital overlap.[5] Similarly, he has shown that ligand associations with pentacyanoferrate(II) are inhibited by inclusion of the iron complex, due to the reduction in the proportion of outer sphere encounters between the reactive species.[6] On the other hand, the Diels–Alder reaction in aqueous solution is catalysed by cyclodextrins, provided that both reactants can fit snugly in the same cyclodextrin cavity.[7] Tee has shown that inclusion of bromide in the cavity of α-cyclodextrin increases its nucleophilic reactivity toward free 4-alkyl-4-bromo-2,5-cyclohexadienones[8] and that the reverse reaction, the bromination of phenols, is also catalysed *via* a pathway involving a cyclodextrin–bromine complex and free phenol.[9,10] The nucleophilic attack of amines on 1-halo-2,4-dinitrobenzenes is catalysed by β-cyclodextrin, and in some cases a pathway whose rate is dependent on the square of the cyclodextrin concentration is observed. This indicates a reaction between a cyclodextrin-substituted benzene complex and a cyclodextrin–amine complex.[11]

In this paper we describe the effect of α-cyclodextrin on the reaction of substituted perbenzoic acids and iodide. The uncatalysed reaction is well characterised,[12] the rate limiting step involves nucleophilic attack of the iodide on the outer peroxidic oxygen of the peracid, this is followed by the formation of $I_2$, which equilibrates with $I_3^-$. The rate is not influenced by salt or solvent effects.[12] The interactions of the substituted perbenzoic acids, and related species, with cyclodextrins is described in the previous paper.[13] The stability constant of the α-cyclodextrin–iodide complex, obtained from conductivity measurements, is 12.4 $dm^3$ $mol^{-1}$.[14]

## Experimental

*Materials.*—The peracids and cyclodextrin are described in the previous paper.[13] The concentrations of stock solutions of the peracids were determined iodometrically and working solutions obtained by dilution. Potassium iodide was purchased from BDH and the sodium acetate and acetic acid buffer components were Analar reagents. Solutions were made up in distilled water.

*Kinetics.*—The reaction of peracid and iodide at 25 °C in acetate buffer, pH 4.8 and ionic strength 0.1 mol $dm^{-3}$, was followed by measuring the absorbance of the product, triiodide anion, at 400 nm, using a High-Tech SF4 stopped-flow spectrophotometer connected to a personal computer fitted with a PCL-812, 12 bit interface card. Unless stated otherwise, the initial concentrations of iodide and peracid were $2 \times 10^{-4}$ and $2 \times 10^{-5}$ mol $dm^{-3}$, respectively, and a pseudo first-order rate constant was obtained from non-linear regression of the monoexponential change in absorbance with time, omitting the data for the first half life of the reaction. The second-order rate constant, $k_{obs}$, is calculated by dividing the observed pseudo first-order rate constant by $1.7 \times 10^{-4}$ mol $dm^{-3}$, the concen-

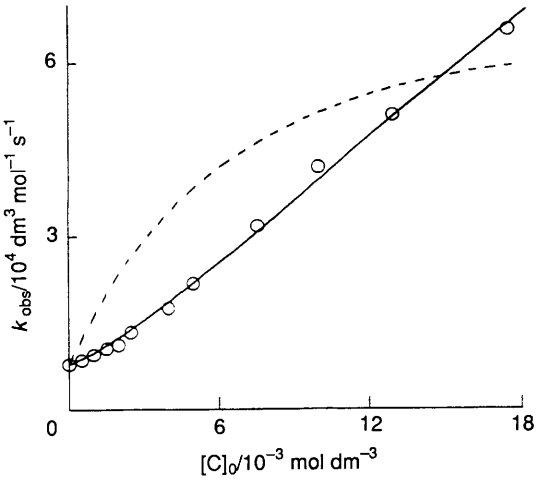



**Fig. 1** Effect of cyclodextrin on the second-order rate constant of the reaction of 4-nitroperbenzoic acid and iodide. The solid curve represents the dependence calculated using eqn. (12) with the best-fit values of the rate constants defined in eqns. (3), (10), and (11). The broken line represents the best-fit dependence when the term second order in cyclodextrin in eqn. (12) is set to zero.

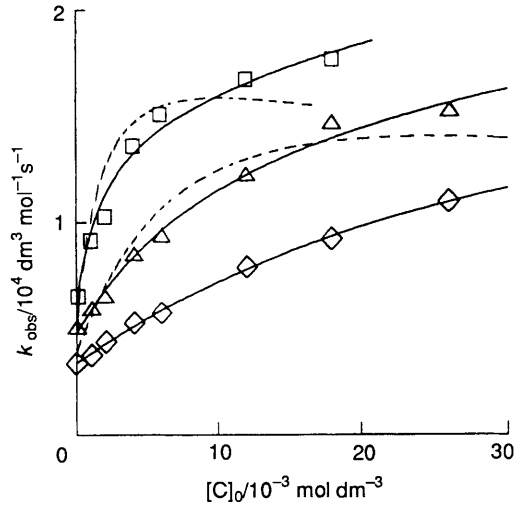



**Fig. 2** Effect of cyclodextrin on the second-order rate constant of the reaction of substituted perbenzoic acids and iodide. The curves are as in Fig. 1; □, 3-Cl; △, 4-$SO_3^-$; ◇, 4-Me.

tration of iodide corrected for reaction with peracid. The average values for three consecutive runs were used to determine $k_{obs}$. The dependence of $k_{obs}$ on the cyclodextrin concentration, $5 \times 10^{-4}$ to $2.6 \times 10^{-2}$ mol dm$^{-3}$, was analysed using the non-linear regression routine of a commercial statistics computer programme.

## Results and Discussion

*Determination of Rate Constants.*—The rate constant for the reaction of 4-nitroperbenzoic acid and iodide, measured under conventional pseudo first-order conditions at four iodide concentrations is $7.97 \times 10^3$ dm$^3$ mol$^{-1}$ s$^{-1}$, in agreement with the value, $7.8 \times 10^3$, published.[12] Figs. 1 and 2 show the effect of the concentration of cyclodextrin on $k_{obs}$, the second-order rate constant for the reaction of the peracids and iodide. The results are consistent with the reaction scheme shown in eqns. (1)–(6), where C is cyclodextrin, P, the peracid, and C,P and C,I$^-$, the cyclodextrin–peracid and cyclodextrin–iodide complexes, whose stability constants $K_P$ and $K_I$ are defined in eqns. (7) and (8).

$$C + P \overset{K_P}{\rightleftharpoons} C,P \quad (1)$$

**Table 1** Stability constants[a] of the peracids and best-fit rate constants, with their standard deviations, according to eqn. (12)

| Peracid | $K_P$/ dm$^3$ mol$^{-1}$ | $k_0/10^3$ dm$^3$ mol$^{-1}$ s$^{-1}$ | $k_{1obs}/10^6$ dm$^6$ mol$^{-2}$ s$^{-1}$ | $k_{2obs}/10^8$ dm$^9$ mol$^{-3}$ s$^{-1}$ |
|---|---|---|---|---|
| 3-Cl | 549 | 6.10 ± 0.68 | 8.58 ± 0.57 | 2.44 ± 0.48 |
| 4-$SO_3^-$ | 99 | 4.77 ± 0.34 | 1.75 ± 0.13 | 0.346 ± 0.066 |
| 4-$NO_2$ | 89 | 7.97 | 2.63 ± 0.22 | 5.00 ± 0.19 |
| 4-Me | 7.3 | 3.34 ± 0.10 | 0.539 ± 0.028 | −0.002 ± 0.011 (*i.e.* < 0.009) |
| 4-Me | 7.3 | 3.39 ± 0.08 | 0.533 ± 0.08 | |
| 4-Me | 8.1 ± 3.0[b] | 3.37 ± 0.10 | 0.544 ± 0.041 | |

[a] The tabulated $K_P$ values are taken from ref. 13 unless stated otherwise. [b] Best-fit value from the kinetic data.

$$C + I^- \overset{K_I}{\rightleftharpoons} C,I^- \quad (2)$$

$$P + I^- \xrightarrow{k_0} \text{Products} \quad (3)$$

$$C,P + I^- \xrightarrow{k_{1a}} \text{Products} \quad (4)$$

$$P + C,I^- \xrightarrow{k_{1b}} \text{Products} \quad (5)$$

$$C,P + C,I^- \xrightarrow{k_2} \text{Products} \quad (6)$$

$$K_P = \frac{[C,P]}{[C][P]} \quad (7)$$

$$K_I = \frac{[C,I^-]}{[C][I^-]} \quad (8)$$

$$k_{obs} = \frac{k_0 + (k_{1a}K_P + k_{1b}K_I)[C]_0 + k_2K_PK_I[C]_0^2}{1 + (K_P + K_I)[C]_0 + K_PK_I[C]_0^2} \quad (9)$$

The reaction scheme leads to the rate law shown in eqn. (9), where $[C]_0$ is the total cyclodextrin concentration, provided that [C,P], [C,I$^-$], and the concentrations of the cyclodextrin complexes of the parent acid and iodine or triiodide products are small compared with $[C]_0$. This holds under the present reaction conditions, where the cyclodextrin is in at least 25-fold excess over the peracid and reaction products, and with the low value[14] of the stability constant of the cyclodextrin–iodide complex, $K_I$, 12.4 dm$^3$ mol$^{-1}$. The observed third- and fourth-order rate constants (first- and second-order in cyclodextrin concentration, respectively), $k_{1obs}$ and $k_{2obs}$, are defined in eqns. (10) and (11) and substituted into eqn. (9) to yield eqn. (12).

$$k_{1obs} \equiv k_{1a}K_P + k_{1b}K_I \quad (10)$$

$$k_{2obs} \equiv k_2K_PK_I \quad (11)$$

$$k_{obs} = \frac{k_0 + k_{1obs}[C]_0 + k_{2obs}[C]_0^2}{1 + (K_P + K_I)[C]_0 + K_PK_I[C]_0^2} \quad (12)$$

The data in Figs. 1 and 2 were fitted to eqn. (12) to yield values of $k_0$, $k_{1obs}$ and $k_{2obs}$, as follows. The values of $K_P$, shown in Table 1 and the value[14] of $K_I$, 12.4 dm$^3$ mol$^{-1}$, (and, for 4-

nitroperbenzoic acid only, the value of $k_0$) are substituted into the equation and the best-fit values of $k_0$ (except in the case of 4-nitroperbenzoic acid where it is determined independently), $k_{1obs}$ and $k_{2obs}$ and their standard deviations are obtained using non-linear regression. The results are shown in the first four rows of Table 1. For 4-methylperbenzoic acid the range of $k_{2obs}$ ± standard deviation includes zero, and when an additional regression is performed, after setting the value $k_{2obs}$ to zero in eqn. (12), an essentially identical fit is obtained as shown in row five of Table 1. The value, $9 \times 10^5$ (see Table 1), is, however, taken as the upper limit of $k_{2obs}$ for 4-methylperbenzoic acid. When $k_{2obs}$ is set to zero in eqn. (12) for the other peracids, a poor fit is obtained (best-fit parameters not shown), represented by the dotted lines in Figs. 1 and 2. Thus the importance of the $k_{2obs}$ term is demonstrated. The sixth row of Table 1 shows the results of a regression analysis of the 4-methylperbenzoic acid data according to eqn. (12) with $k_{2obs}$ set to zero and in which $K_P$ is a fitted parameter. Again there is good agreement, and this serves as a confirmation of the independently determined $K_P$ value for 4-methylperbenzoic acid. On the other hand, the data for 3-chloro- and 4-sulfonatoperbenzoic acids fitted very well to eqn. (12) when the value of $k_{2obs}$ was set to zero, and $K_P$, $k_0$ and $k_{1obs}$ treated as adjustable parameters. Here, the best-fit values of $K_P$ (not shown) were more than three times lower than those measured independently. This illustrates the importance of using stability constants determined by an independent method in the data analysis, because, for the latter two peracids the kinetic behaviour alone gives no indication of the presence of the $k_{2obs}$ term that is second order in cyclodextrin. A pathway whose rate is dependent on the square of the cyclodextrin concentration has been observed, in some cases, for the nucleophilic attack of amines on 1-halo-2,4-dinitrobenzenes.[11] We wonder if there are instances where a relatively minor pathway involving two molecules of cyclodextrin has been overlooked. This situation is indicated if the kinetically determined stability constant is significantly less than that determined by an independent method. In this respect, we doubt whether we would have thought of looking for a second-order term in cyclodextrin for the 3-chloro- and 4-sulfonato-perbenzoic acids if such a term had not been so obviously apparent for 4-nitroperbenzoic acid.

The values of $K_P$ in Table 1 that are used in the data treatment were determined from the effect of cyclodextrin on the pH of a solution containing dilute peracid and its conjugate base in 0.1 mol $dm^{-3}$ sodium nitrate, and are corrected by a factor of 1.14, for competitive binding by the nitrate.[13] These values are appropriate, since the present kinetics were carried out in acetate–acetic acid buffer which does not associate with the cyclodextrin. To confirm this, we have observed (unpublished results) that cyclodextrin does not alter the pH of a dilute solution of acetic acid and its conjugate base, and, hence, neither component binds, or, alternatively, the components have significant, but identical stability constants. The possibility of significant but equal stability constants can be discounted since the acetate anion does not associate with α-cyclodextrin in solution.[14]

*Transition State Pseudoequilibrium Constants.*—The rate constant, $k_0$, of the uncatalysed reaction, eqn. (3), is determined directly. That, $k_2$, of the reaction between the cyclodextrin–iodide complex and the cyclodextrin–peracid complex, eqn. (6), is calculated from $k_{2obs}$ and the stability constants shown in eqn. (11). The pathways involving one molecule of cyclodextrin, represented by eqns. (4) and (5), are kinetically indistinguishable, however, and eqn. (10) shows that $k_{1obs}$ is a composite quantity. Nevertheless, it is possible to probe the structure of the transition state, or states, involving one molecule of cyclodextrin, using the transition state pseudoequilibrium constant approach of Kurtz,[15] adopted for cyclodextrins by Tee.[10] In the present case, the apparent stability (Tee uses dissociation) constants for the transition states of the reactions mediated by one cyclodextrin molecule, hosting the peracid, $[C,P\text{–}I]^‡$, or hosting the iodide, $[P\text{–}C,I]^‡$, formed from the transition state of the uncatalysed reaction, $[P\text{–}I]^‡$, and cyclodextrin, are defined in eqns. (13) and (14), respectively.

$$K_{TS\,1a} = \frac{[[C,P\text{–}I]^‡]}{[[P\text{–}I]^‡][C]} \quad (13)$$

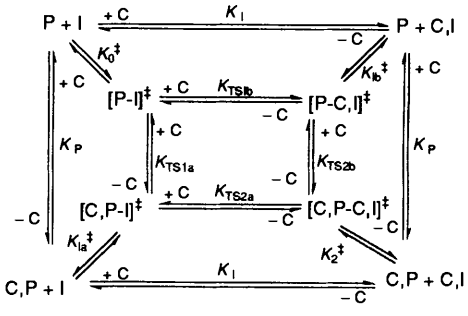
$$K_{TS\,1b} = \frac{[[P\text{–}C,I]^‡]}{[[P\text{–}I]^‡][C]} \quad (14)$$

The corresponding stability constants for the transition state of the reaction mediated by two cyclodextrin molecules, $[C,P\text{–}C,I]^‡$, formed from the transition states involving one molecule of cyclodextrin, and an additional molecule of cyclodextrin, are defined in eqns. (15) and (16).

$$K_{TS\,2a} = \frac{[[C,P\text{–}C,I]^‡]}{[[C,P\text{–}I]^‡][C]} \quad (15)$$

$$K_{TS\,2b} = \frac{[[C,P\text{–}C,I]^‡]}{[[P\text{–}C,I]^‡][C]} \quad (16)$$

A thermodynamic cycle involving the various stability constants is shown in Scheme 1, in which the charge on the




**Scheme 1**

iodide is omitted for clarity. Application of transition state theory to the cycle leads to the relationships shown in eqns. (17) and (18).

$$\frac{k_{1a}K_P + k_{1b}K_1}{k_0} = K_{TS\,1a} + K_{TS\,1b} \quad (17)$$

$$\frac{k_2K_PK_1}{k_{1a}K_P + k_{1b}K_1} = K_{TS\,2a} + K_{TS\,2b} \quad (18)$$

The quantities on the left hand sides of eqns. (17) and (18), respectively, are the ratios of the observed rate constants, $k_{1obs}/k_0$ and $k_{2obs}/k_{1obs}$, as defined in eqns. (10) and (11). Eqns. (17) and (18) are, actually, specific cases of the general relationships, shown in eqns. (19) and (20).

$$\frac{k_{1obs}}{k_0} = \sum K_{TS\,1} \quad (19)$$

$$\frac{k_{2obs}}{k_{1obs}} = \sum K_{TS\,2} \quad (20)$$

**Table 2** Transition state pseudoequilibrium constants, according to eqns. (19) and (20), and stability constants[a] of the parent benzoic acids

| Peracid | $\Sigma K_{TS1}$/dm$^3$ mol$^{-1}$ | $\Sigma K_{TS2}$/dm$^3$ mol$^{-1}$ | $K_{Par}$/dm$^3$ mol$^{-1}$ |
|---|---|---|---|
| 3-Cl | 1410 | 28.4 | 1310 |
| 4-$SO_3^-$ | 367 | 19.7 | 291 |
| 4-$NO_2$ | 329 | 190 | 437 |
| 4-Me | 157 | < 1.5 | 682 |

[a] The tabulated $K_{Par}$ values are taken from ref. 13.

Eqns. (19) and (20) are obtained from a generalised thermodynamic cycle involving the transition state of the uncatalysed reaction and any number of transition states mediated by one and two molecules of cyclodextrin. For example, the pathway shown in eqn. (4), which involves the reaction of cyclodextrin-bound peracid and free iodide, can be subdivided into two possible pathways, one where the percarboxylic acid group protrudes from the wide end of the cyclodextrin cavity, and the other where it is located at the narrow end of the cavity. The usefulness of the transition state pseudoequilibrium constant approach is that the logarithms of the various $K_{TS}$ are directly proportional to the free energy of the stabilisation of the respective transition states due to the cyclodextrin, and hence variations of $\Sigma K_{TS}$ with the nature of the peracid will reflect the variation of the predominant transition state, or states, independently of any postulated mechanism. Thus, the variations of $\Sigma K_{TS1}$ and $\Sigma K_{TS2}$ may be used to probe transition state structure and as a criterion of mechanism. Values of $\Sigma K_{TS1}$ and $\Sigma K_{TS2}$ are shown in Table 2.

Fig. 3 shows the variation of the logarithm of $\Sigma K_{TS1}$ and of $\Sigma K_{TS2}$ with log $K_P$, the stability constant of the cyclodextrin–peracid complex. (The relationship between log $\Sigma K_{TS2}$ and log $K_P$ is discussed in the following paragraph.) With the exception of 4-methylperbenzoic acid, which shows a positive deviation, there is a linear relationship between log $\Sigma K_{TS1}$ and log $K_P$. Here, with the exception of the 4-methylperbenzoic acid, the factors affecting the stability of the transition state involving one molecule of cyclodextrin are similar to those affecting the stability of the cyclodextrin–peracid complex and it follows that the predominant pathway involves the transition state in which the peracid is hosted by the cyclodextrin *i.e.* the pathway shown in eqn. (4). In the previous paper we presented evidence that 4-methylbenzoic acid is included in the cyclodextrin with the methyl group protruding from the wider end of the cavity, while, in contrast, the percarboxylic acid group of 4-methylperbenzoic acid, and of all the other peracids, protrude from the wider end of the cavity.[13] We propose, therefore, that, with the exception of 4-methylperbenzoic acid, the reaction with iodide, mediated by one molecule of cyclodextrin, involves, predominantly, a transition state in which the percarboxylic acid group of the peracid protrudes from the wider end of the cyclodextrin cavity. Fig. 4 shows the relationship between log $\Sigma K_{TS1}$ and the logarithm of the stability constant of the parent benzoic acid, $K_{Par}$, reported in the previous paper,[13] and shown in Table 2. An interesting feature of Fig. 4 is that, again with the exception of 4-methylperbenzoic acid, which now shows a negative deviation, the values of $\Sigma K_{TS1}$ are remarkably similar (see, also, Table 2) to those of $K_{Par}$: the line drawn on Fig. 4 is of unit slope and zero intercept. Since, as reported,[12] and discussed further in the following section, the transition state for the iodide–perbenzoic acid reaction involves proton transfer to the benzoate leaving group, so that the transition state resembles the benzoic acid product, then this resemblance goes even so far as the stability of the respective cyclodextrin inclusion complexes. If the 4-methylperbenzoic acid were to react according to eqn. (4), but *via* the alternative pathway, in which percarboxylic acid group is located at the narrow end of the cyclodextrin cavity, then we would not expect the negative deviation shown in the plot of log $\Sigma K_{TS1}$ against log $K_{Par}$ in Fig. 4. In this case we would expect a positive deviation since the cyclodextrin would not only stabilise the transition state, which resembles the benzoic acid, but also destabilise the ground state, since the peracid would be bound with the energetically less favoured orientation. We conclude, therefore, that the reaction of 4-methylperbenzoic acid and iodide, catalysed by one molecule of cyclodextrin proceeds, predominantly, *via* a cyclodextrin-iodide complex, according to the pathway shown in eqn. (5). This is a similar pathway to that proposed for the reaction of bromide and 4-alkyl-4-bromocyclohexa-2,5-dienones.[8]

In contrast to the $\Sigma K_{TS1}$ values, Fig. 3 shows that there is no systematic relationship between log $\Sigma K_{TS2}$ and log $K_P$. Here the additional stability of the transition state conferred by a second molecule of cyclodextrin would not be expected to correlate with the properties of the peracid, since, if the one molecule of cyclodextrin binds the peracid then the second molecule binds the iodide in the transition state. Moreover, virtually no additional stability is conferred on the transition state for 4-methylperbenzoic acid by a second molecule of cyclodextrin. This is in accord with our conclusion that the transition state for the reaction mediated by just one molecule of cyclodextrin involves the free peracid and the cyclodextrin-iodide complex. In neither case does inclusion of the peracid in the cyclodextrin cavity stabilise the transition state.

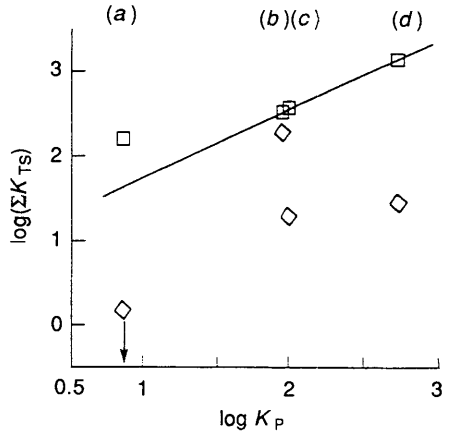



**Fig. 3** Relationship between the log of the transition state pseudo-equilibrium constants, log ($\Sigma K_{TS1}$), □, and log ($\Sigma K_{TS2}$), ◇, defined in eqns. (19) and (20), and the log of the stability constants of the cyclodextrin complexes of substituted perbenzoic acids. (*a*) 4-Me; (*b*) 4-$NO_2$; (*c*) 4-$SO_3^-$; (*d*) 3-Cl.

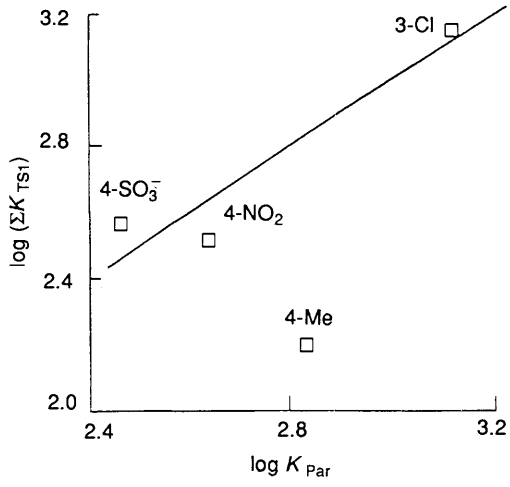



**Fig. 4** Relationship between log ($\Sigma K_{TS1}$), and the log of the stability constant of the cyclodextrin–parent acid complex. The line is drawn with unit slope and zero intercept.

**Table 3** Values[a] of $pK_a$ of the peracid, and calculated kinetic parameters, according to eqns. (11), (25), (26) and (27)

| Peracid | $pK_a$ | $k_2/10^4$ dm$^3$ mol$^{-1}$ s$^{-1}$ | $k_{1a}/10^4$ dm$^3$ mol$^{-1}$ s$^{-1}$ | $k_{1b}/10^4$ dm$^3$ mol$^{-1}$ s$^{-1}$ | % Path 1a |
|---|---|---|---|---|---|
| 3-Cl | 7.53 | 3.58 | 1.51 | 2.54 | 96 |
| 4-$SO_3^-$ | 7.56 | 2.81 | 1.44 | 2.63 | 82 |
| 4-$NO_2$ | 7.14 | 45.3 | 2.74 | 1.60 | 92 |
| 4-Me | 7.86[b] | < 0.88 | 0.91 | 3.76 | 12 |

[a] The tabulated $pK_a$ values are taken from D. M. Davies and P. Jones, *J. Org. Chem.*, 1978, **43**, 769 unless stated otherwise. [b] Ref. 13.

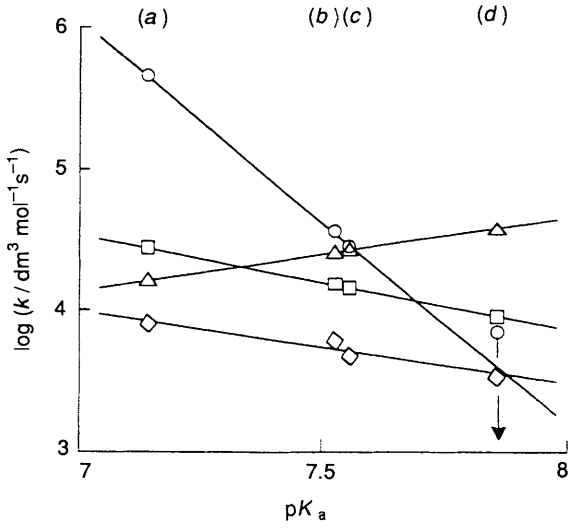



**Fig. 5** Brönsted-type relationships between second-order rate constants and the $pK_a$ of the peracid: ○, $k_2$; □, $k_{1a}$; △, $k_{1b}$; ◇, $k_0$. (*a*) 4-$NO_2$; (*b*) 3-Cl; (*c*) 4-$SO_3^-$; (*d*) 4-Me.

*Brönsted-type Plots.*—Values of $k_2$ were calculated from $k_{2obs}$ and the reactant–cyclodextrin stability constants, according to eqn. (11), and are shown in Table 3 together with the $pK_a$ values of the peracids. Fig. 5 shows the Brönsted-type plots for $k_2$ and also for $k_0$. The data is fitted to eqn. (21), where $k_i^0$ is defined as the rate constant of a hypothetical peracid with $pK_a$, 7.5. This is better, for comparison of the present results, than the standard form of the Brönsted equation that uses the intercept at $pK_a$, 0.

$$\log k_i = \log k_i^0 + \beta_i(pK_a - 7.5) \qquad (21)$$

The rate constants for the uncatalysed pathway conform to eqn. (22), their relationship to the nature of the perbenzoic acid is very similar to that reported previously.[12] The rate constants for the pathway catalysed by two molecules of cyclodextrin conform to eqn. (23) and will be discussed in the following section.

$$\log k_0 = 3.74 - 0.52\,(pK_a - 7.5) \qquad (22)$$

$$\log k_2 = 4.63 - 2.85\,(pK_a - 7.5) \qquad (23)$$

Now, since the rate constants for both the uncatalysed pathway and that catalysed by two molecules of cyclodextrin show a linear free energy relationship with the $pK_a$ of the peracid, it is reasonable to assume that the pathways catalysed by one molecule of cyclodextrin also show such linear free energy relationships. Taking eqn. (21) for $k_{1a}$ and for $k_{1b}$ and raising them to the power 10 and substituting into eqn. (10) gives eqn. (24).

$$k_{1obs} = K_P k_{1a}^0\, 10^{\beta_{1a}(pK_a - 7.5)} + K_I k_{1b}^0\, 10^{\beta_{1b}(pK_a - 7.5)} \qquad (24)$$

Substitution of $K_I$ and, for the respective peracids, $K_P$, $pK_a$, and $k_{1obs}$, into eqn. (24) gives a set of simultaneous equations that is solved numerically for the Brönsted parameters defined in eqn. (21) to give the results shown in eqns. (25) and (26).

$$\log k_{1a} = 4.20 - 0.66(pK_a - 7.5) \qquad (25)$$

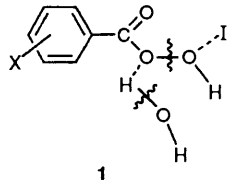
$$\log k_{1b} = 4.39 + 0.52(pK_a - 7.5) \qquad (26)$$

Substitution of the respective $pK_a$ values of the peracids into eqns. (25) and (26) gives the values of $k_{1a}$ and $k_{1b}$ shown in Table 3. Also shown in Table 3 is the quantity % Path 1a calculated using eqn. (27).

$$\%\ \text{Path 1a} = \frac{k_{1a}K_P}{k_{1a}K_P + k_{1b}K_I} = \frac{k_{1a}K_P}{k_{1obs}} \qquad (27)$$

The above quantity is, obviously, the proportion of the overall third-order reaction that goes *via* the pathway shown in eqn. (4), in which the cyclodextrin hosts the peracid in the transition state. The quantity (100 − % Path 1a) represents the proportion of the reaction, eqn. (5), going *via* the transition state in which the cyclodextrin hosts the iodide. Examination of Table 3 leads to the conclusion that the predominant transition state for 4-methylperbenzoic acid involves the interaction of free peracid with the cyclodextrin–iodide complex whereas for the other peracids the predominant transition state involves the interaction of free iodide with the peracid–cyclodextrin complex. This conclusion, obtained by invoking the 'extrakinetic' assumption of a linear free energy relationship, is in accord with the conclusion drawn from consideration of the transition state pseudoequilibrium constants, which are fundamental kinetic parameters that are independent of any postulated mechanism. The Brönsted-type plots for $k_{1a}$ and $k_{1b}$ are shown in Fig. 5.

*Mechanisms.*—The reaction of substituted perbenzoic acids and iodide is well characterised. Substituent effects and solvent isotope effects indicate that the transition state, **1**, unit negative



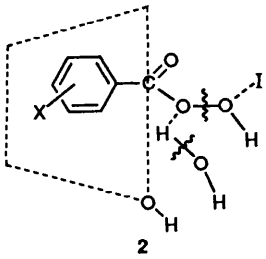

**1**

charge not shown, involves nucleophilic attack of iodide on the outer peroxidic oxygen of the peracid and protonation of the benzoate leaving group by a hydrogen-donor solvent.[12]

The rate constant is independent of ionic strength, and solvent relative permittivity effects are negligible,[12] as is usual for the reaction of an uncharged molecule and a highly polarisable nucleophile.[16] This is convenient for the following discussion because it allows us to eliminate microsolvent effects[1] as a factor in the catalysis by cyclodextrin. The relatively small magnitude of the Brönsted slope, $\beta_0$, −0.52, compared with that of, for example, the reaction of peracids and tertiary amines,[17] might be considered to be indicative of a relatively

small amount of charge transfer from iodide in the transition state. This is unlikely, however, because of the importance of protonation of the benzoate leaving group, as described above, and so the Brönsted slope reflects the opposing substituent effects on iodine–oxygen bond formation and oxygen–oxygen bond breaking, on the one hand, and oxygen–hydrogen bond formation and hydrogen–oxygen bond breaking, on the other, in a transition state that resembles the product, benzoic acid.

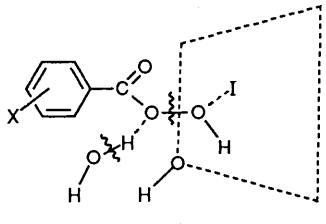
The likely transition state, **2**, unit negative charge not shown (as for all the transition state structures), for the reaction of the peracid–cyclodextrin complex and free iodide is shown schematically below.



**2**

In **2** the peracid takes its favoured orientation, as discussed in the previous paper.[13] Now, if, as discussed above, the transition state of the uncatalysed reaction resembles the product substituted-benzoic acid, then the cyclodextrin can stabilise the transition state **2** by virtue of stabilising the benzoic acid. In accord with this, the stability constants of the respective cyclodextrin–benzoic acid complexes (Table 2) are greater than three times those of the cyclodextrin–perbenzoic acid complexes (Table 1) except in the case of 4-methyl substitution, where the favoured orientation of the benzoic acid is opposite to that of **2**. The latter point has been considered in the section on transition state pseudoequilibrium constants. The Brönsted slope, $\beta_{1a}$, $-0.66$ is similar to $-0.52$, that of the uncatalysed reaction, so that, although the position of the transition state moves away from the products on the reaction coordinate because of the stabilisation of the product by cyclodextrin, the relative extent of oxygen–oxygen bond breaking and oxygen–hydrogen bond formation in **2** is similar to that in **1**. The non-interacting hydroxy group on the cyclodextrin is shown, schematically, in **2** to emphasise that the cyclodextrin is not acting as a particularly better acid catalyst than the water.

The likely transition state, **3**, for the reaction of free peracid and the cyclodextrin iodide complex is shown below, here we

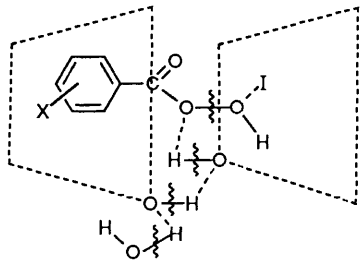


**3**

presume that the iodide is located at the smaller end of the cyclodextrin cavity that constitutes the positive end of its dipole, as suggested by others.[14]

The Brönsted slope, $\beta_{1b}$, $+0.52$, indicates that electron-donating substituents speed up the reaction, and, hence, the transition state involves, predominantly, oxygen–hydrogen bond formation and hydrogen–oxygen bond breaking, with iodide–oxygen bond formation and oxygen–oxygen bond breaking being less important than in **1**. This means that the cyclodextrin enhances the nucleophilicity of the iodide. Tee and Bennett have shown that the reaction of bromide and 4-alkyl-4-bromocyclohexa-2,5-dienones is catalysed by cyclodextrin and conclude that the nucleophilicity of the bromide is enhanced, in some way, by desolvation of the bromide in the cyclodextrin cavity.[8] The same workers have studied the reverse reaction, that of phenols and bromine, and shown that catalysis by cyclodextrin is not consistent with a microsolvent effect due to the less polar cavity of the cyclodextrin than the bulk aqueous medium.[9,10] In the present case of the iodide–peracid reaction, microsolvent effects are unimportant, as discussed above. Also, however, desolvation of the iodide nucleophile is less important than that of bromide, because of the lower charge density of the former. The cyclodextrin mediated enhancement of iodide nucleophilicity is quite unexpected considering that the cyclodextrin must limit the proportion of the iodide surface exposed to the peracid, as is seen by Macartney for outer sphere electron-transfer reactions[5] and also for ligand substitutions.[6] It is possible that the dipole of the cyclodextrin induces a favourable orientation of the peracid (particularly 4-methylperbenzoic acid, with its electron-donating methyl substituent) with respect to the cyclodextrin–iodide complex. We have demonstrated similar dipole effects with site-specific modified cytochrome c.[18] Alternatively, the cyclodextrin may polarise the included iodide and increase its electron density in the direction of its exposed surface at the face of the cyclodextrin cavity. The polarisation of the iodide could either be induced by the overall dipole of the cyclodextrin, or by the lone pairs of each of the six bridging α-(1,4)oxygens, which are located in the middle of the cyclodextrin cavity. The non-interacting hydroxy group on the cyclodextrin is shown, schematically, in **3** as in **2**, to indicate that cyclodextrin is not particularly better than water as an acid catalyst in this transition state.

For the reaction catalysed by two molecules of cyclodextrin the very negative Brönsted slope, $\beta_2$, $-2.85$, indicates that electron-withdrawing substituents speed up the reaction considerably, and, hence, the transition state, **4**, involves iodide–oxygen bond formation and oxygen–oxygen bond-breaking, with oxygen–hydrogen bond formation and hydrogen–oxygen bond breaking being unimportant compared with **1**.



**4**

This means that the two cyclodextrins are acting in concert as an acid catalyst, since neither of the pathways that involve a single cyclodextrin shows a very negative Brönsted slope. The network of hydrogen bonds required for this type of catalysis is shown schematically in **4**. X-Ray crystallography of inclusion complexes shows that the stacking of α-cyclodextrin rings involves hydrogen bonding between primary and secondary cyclodextrin hydroxy groups.[19]

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## References


1 D. W. Griffiths and M. L. Bender, *Adv. Catal.*, 1973, **23**, 209; M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer Verlag, Berlin, 1978.
2 J. Szejtli, *Cyclodextrins and Their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.
3 M. Sakurai, M. Kitagawa, H. Hoshi, Y. Inoue and R. Chujo, *Carbohydr. Res.*, 1990, **198**, 181.
4 W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344.
5 J. A. Imonigie and D. H. Macartney, *Inorg. Chem.*, 1993, **32**, 1007.
6 R. S. Wylie and D. H. Macartney, *Inorg. Chem.*, 1993, **32**, 1830.
7 I. Hunt and C. D. Johnson, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1051.
8 O. S. Tee and J. M. Bennett, *J. Am. Chem. Soc.*, 1988, **110**, 3226.
9 O. S. Tee and J. M. Bennett, *J. Am. Chem. Soc.*, 1988, **110**, 269.
10 O. S. Tee, *Carbohydr. Res.*, 1989, **192**, 181.
11 M. Barra, R. H. de Rossi and E. B. de Vargas, *J. Org. Chem.*, 1987, **52**, 5004; M. Barra and R. H. de Rossi, *J. Org. Chem.*, 1989, **54**, 5020.
12 F. Secco and M. Venturini, *J. Chem. Soc., Perkin Trans. 2*, 1972, 2305.
13 D. M. Davies and J. R. Savage, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1525.
14 J. F. Wojcik and R. P. Rohrbach, *J. Phys. Chem.*, 1975, **79**, 2251.
15 J. L. Kurtz, *J. Am. Chem. Soc.*, 1963, **85**, 985. For a recent discussion, see J. Kraut, *Science*, 1988, **242**, 533.
16 T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper and Row, New York, 3rd edn., 1987.
17 D. M. Davies and R. M. Jones, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1323.
18 J. Butler, S. K. Chapman, D. M. Davies, A. G. Sykes, S. H. Speck, N. Osheroff and E. Margoliash, *J. Biol. Chem.*, 1983, **258**, 6400.
19 K. Harata, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 2066.


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