Effect of α-cyclodextrin on the oxidation of aryl alkyl sulfides by peracids

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Substituent and leaving group effects on the uncatalysed reaction were in good agreement with literature studies. The effect of α-cyclodextrin on the kinetics of aryl alkyl sulfide oxidation by peracids was investigated by studying the following reaction series: (*a*) a range of aryl alkyl sulfides with three different perbenzoic acids and (*b*) a range of alkyl peracids and perbenzoic acids with five different aryl alkyl sulfides. For peracids which bind strongly to α-cyclodextrin, the observed second-order rate constant increases to a maximum with increasing cyclodextrin concentration and thereafter non-productive binding of the sulfide causes a decline in rate. Weakly binding peracids, such as peracetic acid show only a decline in rate constant with increasing cyclodextrin concentration. Linear free energy relationships reveal that transition state stabilisation by one molecule of cyclodextrin shows a far greater dependence on the stability of the peracid–cyclodextrin complex than on the stability of the sulfide–cyclodextrin complex, indicating that the principle pathway for the cyclodextrin mediated reaction is that between the peracid–cyclodextrin complex and uncomplexed sulfide. Additionally, a linear free energy relationship comparing transition state stabilisation for the α-cyclodextrin mediated oxidation of iodide and methyl 4-nitrophenyl sulfide by peracids indicates a common mechanism of catalysis for both substrates, although the catalysis of sulfide oxidation is more effective. Several possible mechanisms of catalysis are discussed. Transition state stabilisation by two molecules of α-cyclodextrin was observed for those peracids which demonstrate significant 2:1 complex formation. Here the principal pathway is the reaction of the 2:1 cyclodextrin–peracid complex with the unbound sulfide, although the extent of transition state stabilisation by the second cyclodextrin molecule is only about the same as its stabilisation of peracid in the ground state.

Introduction

We have recently reported that the α-cyclodextrin mediated reaction between iodide and substituted perbenzoic acids is catalysed by both one and two molecules of cyclodextrin.[1] Enhanced nucleophilicity of the iodide as a result of inclusion in the strongly dipolar cyclodextrin cavity is a possible mechanism for catalysis, as is stabilisation of a transition state resembling the parent benzoic acids, which generally show a strong affinity for α-cyclodextrin.[2] Preliminary results for the oxidation of methyl 4-nitrophenyl sulfide by 4-methyl perbenzoic acid showed that the observed second-order rate constant for sulfide oxidation increased to a maximum with increasing cyclodextrin concentration and subsequently declined.[3] For the peracid–iodide reaction, however, the decline in rate constant was not observed.[1] The binding of aryl alkyl sulfides to α-cyclodextrin exhibits some interesting characteristics. It is likely that, because of unfavourable steric interactions with the 5-H protons within the cyclodextrin cavity, the alkyl sulfide group is located at the wide end of the cyclodextrin cavity.[4] Additionally these compounds generally form strong 2:1 cyclodextrin–guest complexes as well as 1:1 complexes, and in many cases cooperative binding is observed.[4] The second cyclodextrin binds to the alkyl sulfide moiety protruding from the cavity of the first cyclodextrin, with the cyclodextrins probably oriented in a 'head to tail' configuration.[4] For the binding of perbenzoic acids and alkyl percarboxylic acids to cyclodextrin, which has been discussed in the preceding paper,[5] the peroxyacid group is likely to be located at the narrow end of the cavity. 2:1 Complex formation is observed for some of these compounds and is particularly significant for pernonanoic, peroctanoic and *tert*-butyl perbenzoic acids. For 4-methylperbenzoic acid a small second binding step is observed[3] and it is not inconceivable that other perbenzoic acids also form weak 2:1 complexes, even though we have not detected them. The second cyclodextrin is likely to bind to the tail end of the peracid protruding from the wide end of the cyclodextrin cavity.

In this paper we report the full results for the reaction between *p*-substituted aryl alkyl sulfides and substituted perbenzoic acids and alkyl percarboxylic acids. The generally accepted mechanism for sulfide oxidation reactions involving peroxides (YOOH) is nucleophilic attack by the sulfur on the outer peroxidic oxygen of the peroxide, yielding the sulfoxide and the YOH leaving group [eqn. (1)].[6–16]

$$YOOH + SR_2 \longrightarrow YOH + O{=}SR_2 \qquad (1)$$

Electron withdrawing groups at the *para* position in aryl alkyl sulfides reduce the nucleophilicity of the sulfur and, therefore, the rate of reaction,[8–11] whereas for peroxides, the main factor influencing reactivity is the leaving group pK_a,[12,13] with reactivity being greater for peroxides with lower leaving group pK_as. A proton transfer step is also required and it is generally considered that this step occurs in concert with, or subsequent to, the rate limiting oxygen transfer.

Experimental

Materials

Details of α-cyclodextrin and peracids are given in the previous paper.[5] Monoperoxyphthalic acid (40%) was obtained from Interox Chemicals and contained the parent acid as the only significant impurity. The sulfide solutions were prepared and standardised using the method previously described for aryl alkyl sulfides.[4]

Kinetics

Pseudo-first-order rate constants were determined from non-linear regression of the mono exponential decrease in

absorbance with time due to the disappearance of the aryl alkyl sulfide. The reaction was followed at 352 nm for methyl 4-nitrophenyl sulfide, 310 nm for methyl 4-methylsulfanylphenyl ketone, and 260 nm for the other sulfides studied. The reaction was carried out at 25 °C in acetic acid–acetate buffer, pH 4.6 and ionic strength 0.025 mol dm^{-3}. These were the conditions under which the stability constants of the aryl alkyl sulfides were previously measured,[4] and not ionic strength 0.05 mol dm^{-3} as stated in ref. 4. Absorbance changes were followed using an Applied Photophysics SX-17MV stopped-flow spectrophotometer. The concentration of the sulfides ranged from $(1–1.6) \times 10^{-5}$ mol dm^{-3} and the peroxide was in at least thirtyfold excess. The cyclodextrin concentration ranged from $(0.24–38) \times 10^{-3}$ mol dm^{-3}. One syringe contained the sulfide, the cyclodextrin and double strength buffer, whilst the second syringe contained the peracid in distilled water. Observed second-order rate constants were calculated from the quotient of the pseudo-first-order rate constants and the peroxide concentration. For reactions carried out at high cyclodextrin concentration, where the rate of reaction is significantly lower due to non-productive binding of the sulfide, a double exponential change in absorbance was observed when monitored at 260 nm. This was due to slight decomposition of the perbenzoic acids (possibly UV induced decomposition), which absorb at this wavelength. However, decomposition was slow compared to oxidation of the sulfide and the two processes were easily resolved using non-linear regression.

Results

Equilibria and reactions

Our recent work[2–5] has shown that both aryl alkyl sulfides and most peracids form 1:1 inclusion compounds with α-cyclodextrin. In addition, 2:1 cyclodextrin:guest complexes are formed with all of the sulfides and three of the peracids (peroctanoic, pernonanoic and *tert*-butylperbenzoic acid). One of the peracids, the peroxomonosulfate anion, as we have shown from potentiometric studies in the preceding paper,[5] shows no detectable binding with α-cyclodextrin, presumably because of the unfavourable desolvation requirements involved in the inclusion of this charged species. In addition to the cyclodextrin complexes of peracids and of sulfides we must also take into account the complexes with the parent acids, which were present at significant concentrations in the reaction system. This is necessary when calculating the free cyclodextrin concentration when large excesses are not used. Eqns. (2)–(14) describe the equilibria involving the reactants and parent acids, and all the reactions pertinent to this system. In these equations, PH and AH are the protonated forms of the peracid and parent acid respectively and A is the conjugate base of the parent acid.

Peracid–cyclodextrin complexes

$$PH + CD \overset{K_{p11a}}{\rightleftharpoons} PH,CD \quad (2)$$

$$PH,CD + CD \overset{K_{p12a}}{\rightleftharpoons} PH,(CD)_2 \quad (3)$$

Sulfide–cyclodextrin complexes

$$S + CD \overset{K_{s11}}{\rightleftharpoons} S,CD \quad (4)$$

$$S,CD + CD \overset{K_{s12}}{\rightleftharpoons} S,(CD)_2 \quad (5)$$

Equilibria involving the parent acids

$$AH \overset{K_a}{\rightleftharpoons} A + H^+ \quad (6)$$

$$AH + CD \overset{K_{a11a}}{\rightleftharpoons} AH,CD \quad (7)$$

$$AH,CD + CD \overset{K_{a12a}}{\rightleftharpoons} AH,(CD)_2 \quad (8)$$

$$A + CD \overset{K_{a11b}}{\rightleftharpoons} A,CD \quad (9)$$

$$A,CD + CD \overset{K_{a12b}}{\rightleftharpoons} A,(CD)_2 \quad (10)$$

Reactions

$$PH + S \xrightarrow{k_0} Products \quad (11)$$

$$PH,CD + S \xrightarrow{k_{1a}} Products \quad (12)$$

$$PH + S,CD \xrightarrow{k_{1b}} Products \quad (13)$$

$$PH,CD + S,CD \xrightarrow{k_{2a}} Products \quad (14)$$

$$PH,(CD)_2 + S \xrightarrow{k_{2b}} Products \quad (15)$$

$$PH + S,(CD)_2 \xrightarrow{k_{2c}} Products \quad (16)$$

Reactions involving three or more cyclodextrin molecules in the transition state are not included since we have found that the kinetic data is described adequately by eqn. (17) in which only k_0, k_{1obs} and k_{2obs}, the zero-, first- and second-order dependencies on cyclodextrin respectively, are considered. k_{1obs} and k_{2obs} in eqn. (17) are defined by eqns. (18) and (19).

$$k_{obs} = \frac{k_0 + k_{1obs}[CD] + k_{2obs}[CD]^2}{(1 + K_{s11}[CD] + K_{s11}K_{s12}[CD]^2)} \times 1/(1 + K_{p11a}[CD] + K_{p11a}K_{p12a}[CD]^2) \quad (17)$$

$$k_{1obs} = k_{1a}K_{p11a} + k_{1b}K_{s11} \quad (18)$$

$$k_{2obs} = k_{2a}K_{p11a}K_{s11} + k_{2b}K_{p11a}K_{p12a} + k_{2c}K_{s11}K_{s12} \quad (19)$$

In these studies it was necessary to work under conditions in which the cyclodextrin concentration was in less than tenfold excess over the peracid concentration, so it was not possible to use the approximation of $[CD] \cong [CD]_0$, where $[CD]_0$ is the total cyclodextrin concentration, as defined by the mass balance eqn. (20). It was necessary, therefore, to calculate [CD] using an iterative procedure based on eqn. (21) for which the parameters *a*, *b* and *c* are defined by eqns. (22), (23) and (24) respectively. Eqn. (21) is derived from the equilibria relationships for the peracids and the parent acids described by eqns. (2) and (3) and (6)–(10) respectively and from the mass balance equations on cyclodextrin, parent acid and peracid, (20), (25) and (26) respectively. It should be noted that [CD], is the sum of uncomplexed cyclodextrin and that complexed with the acetic acid component of the acetic acid–acetate buffer. Acetic acid has been shown to bind weakly with cyclodextrin[5,17] and we have chosen to express binding constants and transition state pseudo-equilibrium constants in this paper as apparent constants in the presence of 0.025 mol dm^{-3} acetic acid. It should also be noted that the binding constants given in Table 1 in ref. 4 for aryl alkyl sulfides are also apparent binding constants since they were determined in acetate buffer under the same conditions as the present study. The apparent stability constants can be converted to actual stability constants by multiplying by a factor of 1.25 as described in ref. 2.

In eqn. (21), [CD] is calculated as a function of the total cyclodextrin concentration, $[CD]_0$, the total parent acid concentration, $[AH]_0$ and the total peracid concentration, $[PH]_0$ (only the conjugate acid is present under the experimental conditions used). Values for stability constants used in eqn. (21) are taken from our previously determined values,[2–5] correcting to apparent stability constants in the presence of 0.025 mol dm^{-3} acetic acid, as appropriate. Apparent stability constants for the peracids and sulfides are listed in Table 1.

Table 1 Apparent stability constants[a] for the α-cyclodextrin complexes of peracids and aryl alkyl sulfides

Compound	Structure	K_{11}[b]/dm^3 mol^{-1}	K_{12}[b]/dm^3 mol^{-1}	Ref.
Perbenzoic acids				
Perbenzoic acid	C_6H_4–C(O)OOH	316	—[c]	5
4-Methylperbenzoic acid	CH_3–C_6H_4–C(O)OOH	592	8.9	3, 5
4-Nitroperbenzoic acid	NO_2–C_6H_4–C(O)OOH	71	—	2
4-Sulfonatoperbenzoic acid	SO_3^-–C_6H_4C(O)OOH	79	—	2
3-Chloroperbenzoic acid	*m*-Cl–C_6H_4–C(O)OOH	439	—	2
4-*tert*-Butylperbenzoic acid	$(CH_3)_3$C–C_6H_4–C(O)OOH	458	332	5
Monoperoxyphthalic acid	*o*-HO(O)C–C_6H_4–C(O)OOH	Nd[d]	Nd	This work
Other peracids				
Peracetic acid	CH_3C(O)OOH	0.99	—	5
Peroctanoic acid	$CH_3(CH_2)_6$C(O)OOH	186	728	5
Pernonanoic acid	$CH_3(CH_2)_7$C(O)OOH	569	581	5
Peroxomonosulfate	HSO_5^-	—	—	5
Aryl alkyl sulfides				
4-Methoxyphenyl methyl sulfide	CH_3O–C_6H_4–SCH_3	110	200	4
4-Bromophenyl methyl sulfide	Br–C_6H_4–SCH_3	310	430	4
Methyl 4-nitrophenyl sulfide	NO_2–C_6H_4–SCH_3	123	153	4
2-Chloroethyl-4-tolyl sulfide	CH_3–C_6H_4–SCH_2CH_2Cl	73	59	This work
4-Chlorophenyl methyl sulfide	Cl–C_6H_4–SCH_3	154	390	4
Methyl 4-methylsulfanylphenyl ketone	CH_3(O)C–C_6H_4–SCH_3	36	9	This work
Methyl *p*-tolyl sulfide	CH_3–C_6H_4–SCH_3	41	1000	4
4-Methylsulfanylphenylacetic acid	HOOCCH$_2$–C_6H_4–SCH_3	49	73	This work
4-Methylsulfanylaniline	NH_2–C_6H_4–SCH_3	102	9	4

[a] In the presence of 0.025 mol dm^{-3} acetic acid at 25 °C. [b] K_{p11a} and K_{p12a} for peracids and K_{s11} and K_{s12} for sulfides. [c] Indicates that the binding constant was not detectable under conditions employed. [d] Not determined (see text).

$$[CD]_0 = [CD] + [PH,CD] + 2[PH,(CD)_2] + [AH,CD] + 2[AH,(CD)_2] + [A,CD] + 2[A,(CD)_2] \quad (20)$$

$$[CD]_0 = [CD] + [(a + b)[AH]_0 + c[PH]_0] \quad (21)$$

$$a = \frac{2\{H^+\}K_{a11a}K_{a12a}[CD]^2 + 2K_aK_{a11b}K_{a12b}[CD]^2}{\{H^+\}(1 + K_{a11a}K_{a12a}[CD]^2) + K_a(1 + K_{a11b}K_{a12b}[CD]^2)} \quad (22)$$

$$b = \left(\frac{\{H^+\} + K_a - (\{H^+\}K_{a11a}K_{a12a} + K_aK_{a11b}K_{a12b})[CD]^2}{\{H^+\}(1 + K_{a11a}K_{a12a}[CD]^2) + K_a(1 + K_{a11b}K_{a12b}[CD]^2)}\right) \times \left(\frac{\{H^+\}K_{a11a}[CD] + K_aK_{a11b}[CD]}{\{H^+\}(1 + K_{a11a}[CD]) + K_a(1 + K_{a11b}[CD])}\right) \quad (23)$$

$$c = \frac{K_{p11a}[CD] + 2K_{p11a}K_{p12a}[CD]^2}{1 + K_{p11a}[CD] + K_{p11a}K_{p12a}[CD]^2} \quad (24)$$

$$[AH]_0 = [AH] + [A] + [AH,CD] + [AH,(CD)_2] + [A,CD] + [A,(CD)_2] \quad (25)$$

$$[PH]_0 = [PH] + [PH,CD] + [PH,(CD)_2] \quad (26)$$

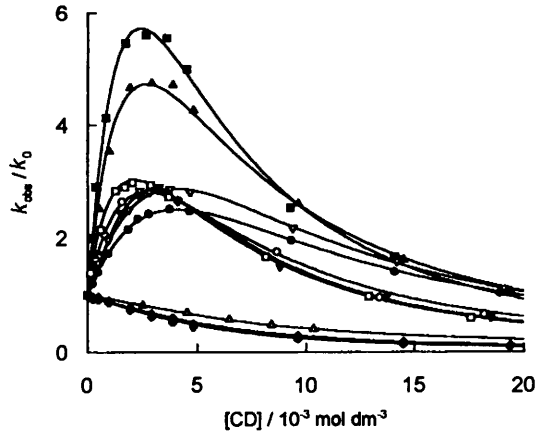


Fig. 1 Plot showing the different effects of α-cyclodextrin concentration on the reaction between methyl 4-nitrophenyl sulfide and various peracids. The symbols are: filled squares, 4-*tert*-butylperbenzoic acid; filled triangles, *m*-chloroperbenzoic acid; open squares, 4-methylperbenzoic acid; open inverted triangles, 4-sulfonatoperbenzoic acid; open circles, perbenzoic acid; filled circles, 4-nitroperbenzoic acid; open triangles, peracetic acid; filled inverted triangles, peroctanoic acid; open diamonds, peroxomonosulfate; filled diamonds, monoperoxyphthalic acid.

Determination of k_0, k_{1obs} and k_{2obs}

Kinetic data for the reaction of a series of peracids with methyl 4-nitrophenyl sulfide and for the reaction of a series of aryl alkyl sulfides with three different peracids are given in Table 2. Values of k_0, the second-order rate constant for the uncatalysed reaction were determined from the quotient of the pseudo-first-order rate constant and the peracid concentration for the reaction between the sulfide and peracid in the absence of cyclodextrin. Fig. 1 shows the different effects of α-cyclodextrin on k_{obs} for the reaction between methyl 4-nitrophenyl sulfide and various peracids. Fig. 2 shows the corresponding plot for the reaction between *m*-chloroperbenzoic acid and several aryl alkyl sulfides. Values for k_{1obs} and k_{2obs}, the first- and second-order dependencies on cyclodextrin respectively were determined from non-linear least-squares analysis using eqn. (17), in which k_0, K_{p11a}, K_{p12a}, K_{s11} and K_{s12} were constants taken from Tables 1 and 2. The curves in Figs. 1 and 2 are the best fits to eqn. (17) using the stability constants and parameters listed in Tables 1 and 2. Fig. 1 shows that, for peracids which bind strongly to cyclodextrin, the observed second-order rate constant increases to a maximum with increasing cyclodextrin concentration and thereafter declines. Weakly binding peracids, such as peracetic acid and peroxomonosulfate show only a decline in rate constant with increasing cyclodextrin concentration. Fig. 2 shows the effect on the curves of the different strengths of complex formation between cyclodextrin and aryl alkyl sulfides. The shape and height of the peaks are determined by the strength of association between the sulfides and cyclodextrin, with 4-bromophenyl methyl sulfide which forms strong 1:1 and 2:1 complexes, having a small sharp peak, whereas methyl 4-methylsulfanylphenyl ketone, which forms weak 1:1 and 2:1 complexes, has a large broad peak.

Table 2 Rate constants and transition state pseudoequilibrium constants (±standard deviation) for the reaction of peracids with aryl alkyl sulfides in the presence of α-cyclodextrin at 25 °C in acetic acid acetate buffer, pH 4.6, 0.025 mol dm^{-3} ionic strength

Compound	k_0/dm^3 mol^{-1} s^{-1}	k_{1obs}/10^3 dm^6 mol^{-2} s^{-1}	k_{2obs}/10^6 dm^9 mol^{-3} s^{-1}	K_{TS1}[a]/dm^3 mol^{-1}	K_{TS2}[a]/dm^3 mol^{-1}
Reaction of peracids with methyl 4-nitrophenyl sulfide					
Perbenzoic acid	28	69 ± 1	—	2452 ± 22	—
4-Methylperbenzoic acid	21.4	83 ± 2	0.29 ± 0.23	3813 ± 106	3.1 ± 2.5
4-Nitroperbenzoic acid	78.6	92.0 ± 0.5	0.38 ± 0.06	1171 ± 6	4.1 ± 0.5
4-Sulfonatoperbenzoic acid	47.1	68.0 ± 0.6	—	1458 ± 13	—
3-Chloroperbenzoic acid	52.7	273 ± 4	13.2 ± 7.7	5186 ± 82	48 ± 28
4-*tert*-Butylperbenzoic acid	24.4	144 ± 3	37 ± 1.4	5909 ± 130	257 ± 10
Monoperoxyphthalic acid[b]	196	—	—	—	—
Peracetic acid	7.2	0.45 ± 0.01	—	62.2 ± 1.3	—
Peroctanoic acid	9.6	12.4 ± 2.5	7.64 ± 3.3	1298 ± 226	613 ± 266
Pernonanoic acid	10.8	19.4 ± 1.3	18.9 ± 6.8	1793 ± 116	976 ± 352
Peroxomonosulfate	110	1.85 ± 0.29	—	17.2 ± 2.6	—
Reaction of aryl alkyl sulfides with 3-chloroperbenzoic acid					
4-Methoxyphenyl methyl sulfide	1002	5078 ± 214	279 ± 33	5067 ± 214	55 ± 7
4-Bromophenyl methyl sulfide	333	1396 ± 24	—	4192 ± 72	—
Methyl 4-nitrophenyl sulfide	52.7	273 ± 4	13.2 ± 7.7	5186 ± 82	48 ± 28
2-Chloroethyl-4-tolyl sulfide	329	1670 ± 40	—	5076 ± 123	—
4-Chlorophenyl methyl sulfide	312	1520 ± 60	16.7 ± 14.4	4634 ± 183	11.0 ± 9.5
Methyl 4-methylsulfanylphenyl ketone	132	766 ± 16	—	5955 ± 60	—
Methyl *p*-tolyl sulfide	701	3680 ± 40	69 ± 0.8	5183 ± 56	18.7 ± 0.3
4-Methylsulfanylphenylacetic acid[c]	505	2760 ± 70	—	5433 ± 138	—
4-Methylsulfanylaniline[d]	1353	7960 ± 80	42 ± 7	5958 ± 60	5 ± 1
Reaction of aryl alkyl sulfides with 4-methylperbenzoic acid					
4-Bromophenyl methyl sulfide	161	521 ± 14	—	3240 ± 90	—
Methyl 4-nitrophenyl sulfide	21.4	83 ± 2	0.29 ± 0.23	3813 ± 106	3.1 ± 2.5
4-Chlorophenyl methyl sulfide	181	55 ± 1	—	3044 ± 38	—
Methyl 4-methylsulfanylphenyl ketone	55.0	278 ± 11	—	4620 ± 69	—
Methyl *p*-tolyl sulfide	340	1280 ± 22	36 ± 6	3765 ± 65	28.1 ± 4.7
Reaction of aryl alkyl sulfides with 4-nitroperbenzoic acid					
4-Bromophenyl methyl sulfide	385	401 ± 25	15.8 ± 7.2	1042 ± 65	39 ± 17.8
Methyl 4-nitrophenyl sulfide	78.6	92.0 ± 0.5	0.38 ± 0.06	1171 ± 6	4.1 ± 0.5
4-Chlorophenyl methyl sulfide	518	487 ± 14	—	940 ± 26	—
Methyl 4-methylsulfanylphenyl ketone	145	210 ± 6	—	1448 ± 17	—
Methyl *p*-tolyl sulfide	723	785 ± 2	17.6 ± 2.5	1086 ± 2	22 ± 3

[a] Values for transition state pseudoequilibrium constants are apparent values in the presence of 0.025 mol dm^{-3} acetic acid at 25 °C, unless otherwise stated. [b] Conducted in 0.025 mol dm^{-3} sulfuric acid, pH 1.6. [c] Conducted in 0.02 mol dm^{-3} sulfuric acid, pH 1.7. [d] Conducted in acetic acid-acetate buffer, pH 6.0, 0.05 mol dm^{-3} ionic strength.

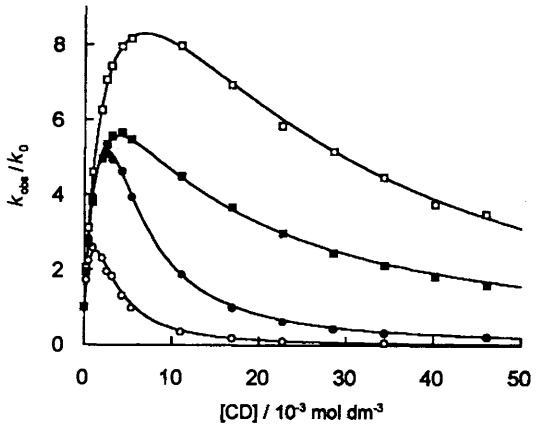


Fig. 2 Plot showing the different effects of α-cyclodextrin concentration on the reaction between *m*-chloroperbenzoic acid and four different *p*-substituted aryl alkyl sulfides. Symbols are: open squares, methyl 4-methylsulfanylphenyl ketone; filled squares, 4-methylsulfanylaniline; filled circles, methyl *p*-tolyl sulfide; open circles, 4-bromophenylmethyl sulfide.

In several cases nonsensical results were obtained, *i.e.* negative rate constants, when trying to fit to both k_{1obs} and k_{2obs}, in eqn. (17) and so in these cases k_{2obs} was set to zero. In the majority of other cases k_{2obs} was generally small, the exception being those reactions involving peracids which demonstrate significant 2:1 complex formation. This raises the question of the significance of the inclusion, or not, of a k_{2obs} term on the determination of a value for k_{1obs}. In cases where the existence of a k_{2obs} term is questionable, such as in the reaction of methyl *p*-tolyl sulfide with *m*-chloroperbenzoic acid it is clear from Fig. 3(*a*) that little difference is made to the best fit curve when fitting with k_{2obs} set to zero. More importantly, the value obtained for k_{1obs} is relatively unaffected, increasing only slightly (6.5%). This is typical of most of the reactions studied and so we can conclude that even if second-order dependencies do in fact exist in those cases where we have used eqn. (17) with k_{2obs} set to zero, it is unlikely to affect the determined value of k_{1obs} significantly. This contrasts with the situation for the reactions of methoxyphenyl methyl sulfide with *m*-chloroperbenzoic acid, and methyl 4-nitrophenyl sulfide with *tert*-butyl perbenzoic acid as shown in Fig. 3(*b*) and (*c*) respectively. Here it is clear that the data cannot be adequately described without a k_{2obs} term. This is also true of the reactions of peroctanoic and pernonanoic acid with methyl 4-nitrophenyl sulfide.

In the case of the reaction of monoperoxyphthalate with methyl 4-nitrophenyl sulfide no k_{1obs} or k_{2obs} terms are required to describe the data, with the k_{obs} dependency on cyclodextrin being simply a function of k_0 and the stability constants for the sulfide. The value of the stability constant for the cyclodextrin–

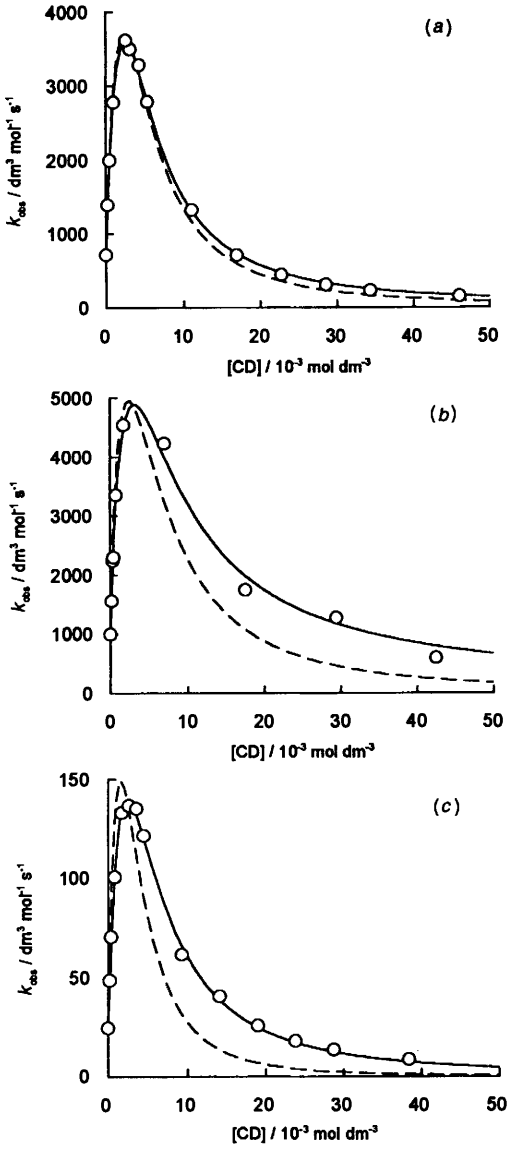


Fig. 3 Comparison of best fits to eqn. (17) for the cyclodextrin mediated reactions between (*a*) methyl *p*-tolyl sulfide and *m*-chloroperbenzoic acid, (*b*) 4-methoxyphenyl methyl sulfide and *m*-chloroperbenzoic acid and (*c*) methyl 4-nitrophenyl sulfide and 4-*tert*-butylperbenzoic acid. The solid lines are best fits to eqn. (17) when k_{2obs} is allowed to float as a parameter, whereas the dotted lines are the corresponding fits when k_{2obs} is set to zero.

peracid complex was not determined in this case because of the complicating factor of the *ortho* carboxylic acid group however, the good fit obtained to the data with K_{p11a} set to zero indicates that this parameter is very small (Fig. 1).

One final point concerning the curve fitting is the observation that for three of the aryl alkyl sulfides, methyl 4-methylsulfanylphenyl ketone, 4-methylsulfanylphenylacetic acid and 2-chloroethyl 4-tolyl sulfide, the data could not be adequately described by using the independently determined[4] K_{s11} and K_{s12} values. Fig. 4 shows the example of methyl 4-methylsulfanylphenyl ketone in which the dashed line is the best fit to eqn. (17) using stability constants of 9 and 0.4 dm^3 mol^{-1} for K_{s11} and K_{s12} respectively, which were taken from ref. 4. k_{2obs} was set to zero in this case since a negative value was returned if it was allowed to float. Clearly the best fit curve describes the data very poorly, with the most likely reason being the use of erroneous K_{s11} and K_{s12} values. Our original determination of stability constants for 1:1 and 2:1 complexes of cyclodextrin with methyl 4-methylsulfanylphenyl ketone using the spectrophotometric titration technique was difficult since very little of the 2:1 complex was present even at the

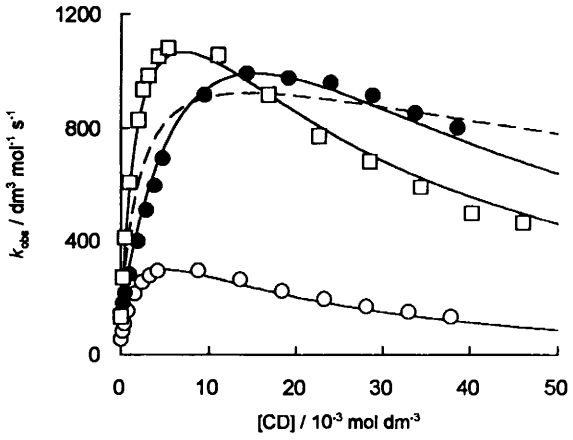


Fig. 4 Effect of cyclodextrin concentration on the observed second-order rate constant, k_{obs}, for the reaction between methyl 4-methylsulfanylphenyl ketone and *m*-chloroperbenzoic acid (open squares), 4-nitroperbenzoic acid (filled circles) and 4-methylperbenzoic acid (open circles). The lines are best fits to eqn. (17) using global regression analysis on data from all three reactions, in which K_{s11} and K_{s12} were parameters and k_{2obs} was set to zero. The dotted line is the best fit obtained for the reaction of methyl 4-methylsulfanylphenyl ketone and *m*-chloroperbenzoic acid with k_{2obs} set to zero and using the stability constants for methyl 4-methylsulfanyl ketone listed in ref. 4.

highest cyclodextrin concentration used (this was also true of 2-chloroethyl 4-tolyl sulfide). In light of this, K_{s11} and K_{s12} were included as parameters in eqn. (17) and a global regression analysis was performed on data from the reactions of methyl 4-methylsulfanylphenyl ketone with 3-chloroperbenzoic acid, 4-methyl perbenzoic acid and 4-nitroperbenzoic acid. The solid lines in Fig. 4 show the resulting best fit curves obtained.

The kinetically determined values of K_{s11} and K_{s12}, were 35.5 ± 4 and 9 ± 4 respectively. Kinetically determined K_{s11} and K_{s12} values were also obtained for 4-methylsulfanylphenylacetic acid and 2-chloroethyl 4-tolyl sulfide, using the same procedure, although in these cases data was only available for the reaction with one peracid, 3-chloroperbenzoic acid. These values are listed in Table 3 and replace the corresponding values listed in Table 1 in ref. 4.

If the original spectrophotometric titration data for these three sulfides are then analysed according to eqn. (27)[4] with the

$$\frac{A(\lambda_i)}{[S]_0} = \frac{\varepsilon_0(\lambda_i) + \varepsilon_{11}(\lambda_i)K_{s11}[CD]_0 + \varepsilon_{12}(\lambda_i)K_{s11}K_{s12}[CD]_0^2}{1 + K_{s11}[CD]_0 + K_{s11}K_{s12}[CD]_0^2} \quad (27)$$

kinetically determined K_{s11} and K_{s12} values included as constants, then very good fits are obtained, as shown in Fig. 5 for methyl 4-methylsulfanylphenyl ketone. This was done for all three of the sulfides and Table 3 lists the calculated molar absorbtivities of the 1:1 and 2:1 complexes at λ_{max}. These values replace those listed in Table 1 in ref. 4.

Of the three sulfides for which we have determined stability constants from kinetic data, the biggest discrepancy with spectrophotometrically determined stability constants was for 4-methylsulfanylphenylacetic acid (K_{s11} = 520 ± 260 and 49 ± 9 from spectrophotometric titration and kinetic method respectively). In this case the difficulty in obtaining a reliable value from the spectrophotometric titration technique can be ascribed to the fact that the spectra for the 1:1 and 2:1 complexes were very similar (see Table 3). For the remaining aryl alkyl sulfides used in this study the independently determined values[4] were wholly consistent with the kinetics.

Discussion

Uncatalysed reactions

There is a linear dependence (not shown) of log k_0 on σ_p[18] for the reaction of a range of aryl alkyl sulfides with

Table 3 λ_{max} values, molar absorbivities and apparent stability constants[a] for three aryl alkyl sulfides, calculated from kinetic and spectrophotometric titration data. Determinations were carried out at 25 °C in acetic acid–acetate buffer, pH 4.6, 0.025 mol dm^{-3} ionic strength, unless otherwise stated. Original values determined from spectrophotometric titration data only (ref. 4) are given in parentheses

Sulfide	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}	K_{11}/dm^3 mol^{-1}	1:1 λ_{max}/nm	1:1 ε/dm^3 mol^{-1} cm^{-1}	K_{12}/dm^3 mol^{-1}	2:1 λ_{max}/nm	2:1 ε/dm^3 mol^{-1} cm^{-1}
2-Chloroethyl-4-tolyl sulfide	254	8 100	73 ± 9 (71 ± 10)	254 (256)	6 300 (7 000)	59 ± 11 (23 ± 4)	258 (260)	10 400 (12 200)
4-Methyl methylsulfanyl-phenyl ketone	310	17 500	36 ± 4 (9 ± 5)	312 (314)	16 300 (15 900)	9 ± 4 (0.4 ± 19)	316 (316)	19 900 (33 600)
4-Methylsulfanylphenyl-acetic acid	256	11 800	49 ± 9 (520 ± 260)	260 (256)	10 400 (11 400)	73 ± 18 (90 ± 70)	260 (260)	10 800 (10 700)

[a] Applies where the stability constant was determined in acetic acid–acetate buffer. See text for details.

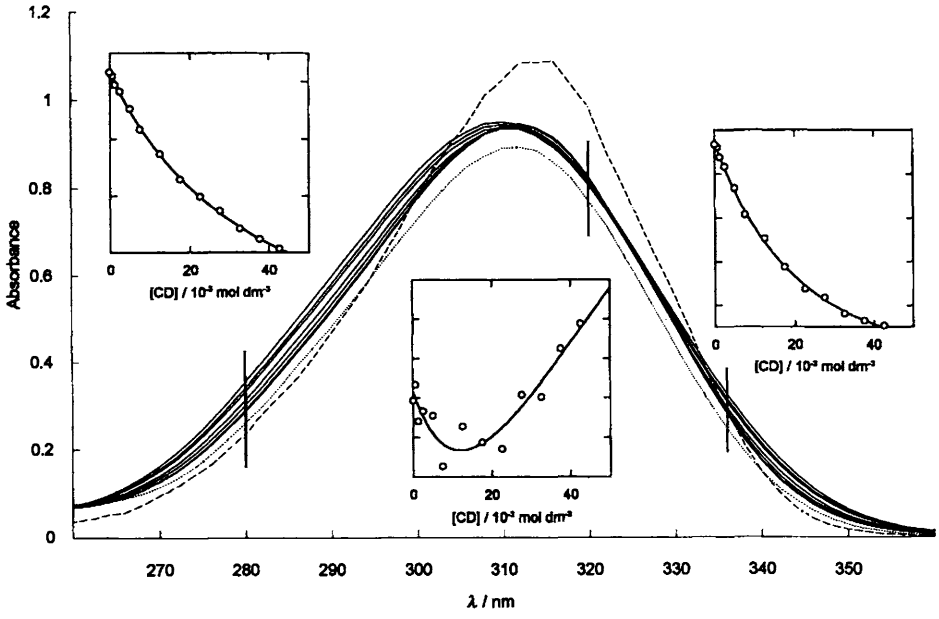


Fig. 5 Effect of α-cyclodextrin concentration on the spectrum of 5.0 × 10^{-5} mol dm^{-3} methyl 4-methylsulfanylphenyl ketone at 25 °C in acetic acid–acetate buffer, pH 4.6, ionic strength 0.025 mol dm^{-3}. The dotted and broken lines are, respectively, the calculated spectra of the 1:1 and 2:1 cyclodextrin–guest complexes. The insets are examples of the best fits to eqn. (27) at 280, 320 and 336 nm.

m-chloroperbenzoic acid, with the exception of 4-methylsulfanylaniline ($\sigma_p = -0.66$[18]) which is an obvious outlier and was excluded, yielding a Hammett ρ value of -1.15 ± 0.08. Similarly, for 4-nitroperbenzoic acid and 4-methylperbenzoic acid, ρ-values of -1.09 and -1.13, respectively, were obtained.

A plot (not shown) of log k_0 *vs.* pK_a(YOH), using the conventions of eqn. (1), yielded $\beta_{lg} = -0.65 \pm 0.06$ for methyl 4-nitrophenyl sulfide, which is based on ten peracids, excluding the outlier, HSO_5^- (Bunton has obtained a similar rate constant for this reaction).[11] This value of β_{lg} is in good agreement with that obtained by Bruice for the reaction of thioxane in *tert*-butyl alcohol with a range of peroxides, spanning a pK_a range for the YOH leaving group of 4 to 17.[12]

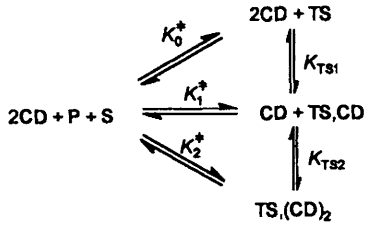
Reactions mediated by cyclodextrin

Eqns. (11)–(16) detail the possible pathways for the oxidation of sulfides by peracids in the presence of cyclodextrin. For the first order dependence on cyclodextrin, because the pathways k_{1a}, k_{1b} and k_{1c} cannot be distinguished kinetically we use the composite quantity k_{1obs} in eqn. (17), and, likewise, for the second-order dependence on cyclodextrin we use k_{2obs}. Even the pathways detailed in eqns. (11)–(16) oversimplify the situation since (*a*) for each of the reactants there are two main binding conformations *i.e.* the sulfide or peroxy acid group can each be located either at the wide or narrow end of the cyclodextrin cavity and (*b*) limited enantioselectivity has been observed for this type of reaction under certain conditions,[19,20] although enantiomeric excesses are significantly lower for α-cyclodextrin compared to β-cyclodextrin.[21]

The transition state pseudoequilibrium approach, developed for enzymology by Kurz[22] and adapted for cyclodextrin mediated reactions by Tee,[23] is ideal for the analysis of multiple pathway reaction systems. The simple thermodynamic cycle shown in Scheme 1 represents the situation for the reaction of aryl alkyl sulfides with peracids in the presence of cyclodextrin. Application of transition state theory to the cycle leads to the relationships shown in eqns. (28) and (29), in which the

$$K_{TS1} = \frac{K_1^{\ddagger}}{K_0^{\ddagger}} = \frac{k_{1obs}}{k_0} \quad (28)$$

$$K_{TS2} = \frac{K_2^{\ddagger}}{K_1^{\ddagger}} = \frac{k_{2obs}}{k_{1obs}} \quad (29)$$



Scheme 1

transition state pseudoequilibrium constants, K_{TS1} and K_{TS2}, are measures of the stabilisation imparted to the transition state as a result of its association with one and two molecules of cyclo-

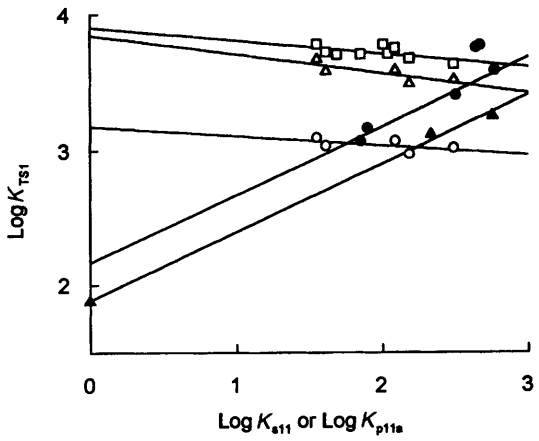


Fig. 6 Linear free energy relationships: open symbols, correlation between log K_{TS1} and log K_{s11}. Filled symbols, correlation between log K_{TS1} and log K_{p11a}. The series represented by the symbols are: open squares, reaction of *m*-chloroperbenzoic acid with a range of aryl alkyl sulfides (slope ± sd = −0.10 ± 0.05); open triangles, reaction of 4-methylperbenzoic acid with a range of aryl alkyl sulfides (−0.14 ± 0.06); open circles, reaction of 4-nitroperbenzoic acid with a range of aryl alkyl sulfides (−0.07 ± 0.06); filled circles, reaction of methyl 4-nitrophenyl sulfide with a range of substituted perbenzoic acids (0.51 ± 0.05, excluding the outliers, *tert*-butylperbenzoic acid and *m*-chloroperbenzoic acid); filled triangles, reaction of methyl 4-nitrophenyl sulfide with a range of alkyl peracids (0.51 ± 0.03).

dextrin respectively irrespective of the actual pathways from reactants to products and independent of any equilibria between cyclodextrin and the peracids or sulfides that do not lead to a transition state, *i.e.* independent of any non-productive binding.

The logarithms of the transition state pseudoequilibrium constants are proportional to the Gibbs free energy of stabilisation of the transition state by cyclodextrin, and a comparison of this quantity with other free energy parameters can give information about the structure of the transition state. Thus, the relative sensitivity of K_{TS} to changes in substrate structure allows us to gain an insight into the mode of binding in the activated complex. There are several examples of this in the literature.[24,25]

Fig. 6 shows correlations between log K_{TS1} and the log of stability constants of both peracid and sulfide complexes with cyclodextrin. The three sets of data shown as open symbols correspond to the reaction of a series of aryl alkyl sulfides with three substituted perbenzoic acids, in which log K_{TS1} has been plotted against the log of the stability constant of the sulfide–cyclodextrin complex, K_{s11}. The filled symbols correspond to the reaction of a series of alkyl peracids and a series of substituted perbenzoic acids with methyl 4-nitrophenyl sulfide. The alkyl peracids and perbenzoic acids do not appear to belong to the same series. The slopes for the linear fits are given in the caption to Fig. 6.

It is evident from Fig. 6 that the degree of transition state stabilisation by one molecule of cyclodextrin shows a far greater dependence on the strength of the peracid–cyclodextrin complex than on the strength of the sulfide–cyclodextrin complex, for which there is a small negative slope. This sensitivity of K_{TS1} towards the strength of the peracid–cyclodextrin complex suggests that the predominant transition state structure involving one molecule of cyclodextrin resembles a peracid–cyclodextrin complex reacting with uncomplexed sulfide as shown in **1**. Structure **1** is drawn with the peroxide group at the narrow end of the cavity, which is the preferred orientation of peroxides within α-cyclodextrin, as discussed in the previous paper.[5] Despite this configuration, the outer peroxidic oxygen of the peracid is located right at the rim of the cavity and should, therefore, be available to undergo reaction with the sulfide.

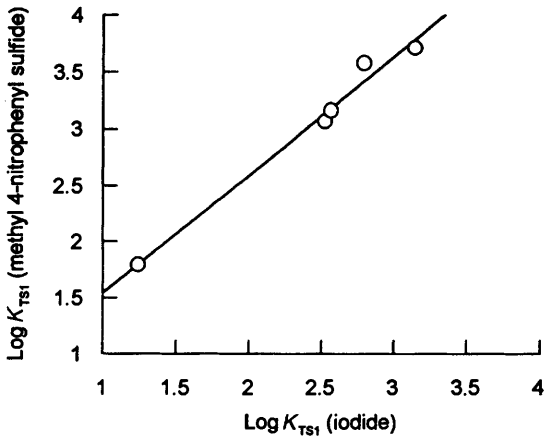
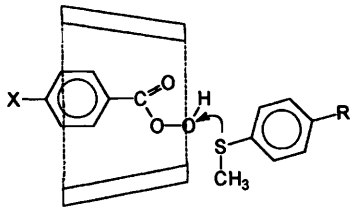


Fig. 7 Comparison of log K_{TS1} values for the α-cyclodextrin mediated oxidation of methyl 4-nitrophenyl sulfide and iodide by peracids



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The small negative correlation of log K_{TS1} and log K_{s11} indicates that a small proportion of the overall sulfide oxidation reaction process *via* the k_{1b} pathway, as might be expected in view of the observation of a small degree of enantioselectivity for these types of reactions under certain conditions.[21]

Comparison with the peracid–iodide reaction

In Fig. 7, log K_{TS1} values for the reaction of methyl 4-nitrophenyl sulfide with various peracids (in order of increasing log K_{TS1}: peracetic, 4-nitroperbenzoic, 4-sulfonatoperbenzoic 3-chloroperbenzoic and 4-methylperbenzoic) have been plotted against K_{TS1} values for the corresponding reactions with iodide.[1] The slope of 1.04 indicates that the mechanism of catalysis of these reactions by cyclodextrin is common to both sulfide and iodide, whereas the position of the intercept shows that catalysis is more effective for the sulfide oxidation. We have shown that the main pathway for the catalysed oxidation of aryl alkyl sulfides involves the cyclodextrin peracid complex reacting with unbound sulfide, and it follows from Fig. 7 that an analogous situation exists for iodide.

The stabilisation of the transition state of a reaction involving a peracid molecule bound in the cyclodextrin cavity with the peracid oxygen located at the narrow end of the cavity may be due to a number of factors. These include the microsolvent effect of the cyclodextrin cavity,[26] desolvation of the peracid[6] as a result of inclusion within the cyclodextrin cavity,[27] acid–base catalytic effects by the relatively conformationally free primary OH groups of the cyclodextrin or stabilisation of a parent acid-like transition state.[1] Yoshida has identified factors contributing to the activation process for the directional inclusion of 2-naphthylazophenol guest molecules in α-cyclodextrin.[28] Similar factors may be important in the present case, with the positively charged end of the cyclodextrin dipole attracting the nucleophile to the outer peroxide oxygen at the narrow end of the cavity.

Effect of two molecules of cyclodextrin

K_{TS2} values are, for the majority of cases, very small. Only where there is significant 2:1 cyclodextrin–peracid complex formation, such as for 4-*tert*-butylperbenzoic acid, peroctanoic

acid and pernonanoic acid, do we observe large K_{TS2} values. It is probable that the predominant activated complex involving two cylcodextrin molecules in these cases resembles the 2:1 cyclodextrin–peracid complex reacting with uncomplexed sulfide. This is supported by a comparison of K_{p12a} and K_{TS2} values in Tables 1 and 2, which shows that the second cyclodextrin molecule stabilises the transition state to the same extent as it stabilises the peracid in the ground state. The second cyclodextrin molecule, therefore, performs no catalytic function—it is bound to the alkyl chain of the alkyl peracids or to the *tert*-butyl group of 4-*tert*-butylperbenzoic acid, as described in the preceding paper,[5] but does not participate in the reaction. This could be termed 'neutral binding', as opposed to 'positive binding', which occurs for the cyclodextrin molecule in which the peroxide group is located, and 'non-productive binding', which occurs for the 1:1 and 2:1 complexes of cyclodextrin with sulfides.

Tables 1 and 2 also show that in many cases small K_{TS2} values were obtained, despite the fact that a second binding step was not detected for the peracids involved (the exception being 4-methylperbenzoic acid where a small K_{p11a} term was determined). In these cases it is probable that the small K_{TS2} values reflect an activated complex in which both reactants are in the form of 1:1 complexes with cyclodextrin as given in eqn. (14). For the oxidation of iodide by substituted perbenzoic acids in the presence of cyclodextrin, significant K_{TS2} values were observed in all cases, yet except for 4-methylperbenzoic acid, which binds weakly to a second cyclodextrin molecule, all of the perbenzoic acids used in that study formed 1:1 complexes only. We proposed that these K_{TS2} values also reflected the reaction of bound peracid with bound iodide.[1,3]

Non-productive binding

The fall in rate constant that is observed without exception at high cyclodextrin concentrations, as shown in Figs. 1 and 2, is due to the binding of either the first and/or second cyclodextrin to the sulfide, and is a manifestation of non-productive binding. The shape and height of the peaks in Fig. 2 are determined by the strength of the 1:1 and 2:1 complexes between the sulfides and cyclodextrin. The observation of non-productive binding for the 2:1 cyclodextrin–sulfide complexes is not surprising since the second cyclodextrin effectively shields the sulfur atom from the peracid.[4] For 1:1 complexes, in which the alkyl sulfide group should be exposed at the wide end of the cyclodextrin cavity,[4] the steric or electrostatic factors causing the lowered reactivity of the sulfide are not obvious.

We are now extending this work to look at these reactions with β-cyclodextrin, and also the cyclodextrin mediated reaction between aryl alkyl sulfoxides and peracids.

Acknowledgements

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