Acyl Transfer Reactions Mediated by Cyclodextrins. The Reaction of External Nucleophiles with Encapsulated Alkanoate Esters of varying Chain Length

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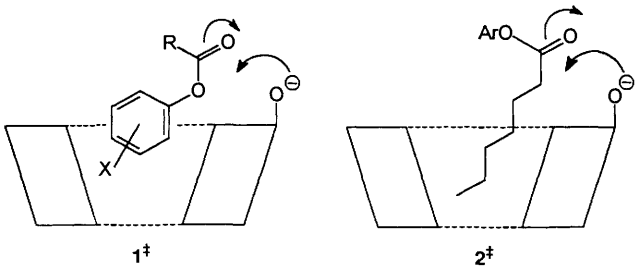
The kinetics of the reaction of *p*-nitrophenyl alkanoates (acetate to decanoate, C_2 to C_{10}) with trifluoroethanol (TFE) in the presence of α-, β-, or hydroxypropyl-β-cyclodextrin (α-, β-, or Hp-β-CD) in basic aqueous solution have been measured. The results are analysed to afford rate constants for nucleophilic attack on the free and CD-bound esters (k_N and k_{cN}, respectively). Generally speaking, the values of k_N and k_{cN} are not very different, so that binding the esters to CDs has only modest effects on their reactivities towards TFE, reacting as its anion. However, there is a general trend in k_{cN} values such that transition-state stabilization increases in a biphasic manner as the alkanoate chain is lengthened from C_2 to C_{10}. For short chains ($< C_7$) the rise in transition stabilization is gentle but for longer chains ($> C_6$) is quite steep. This same behaviour is observed for all three CDs, with only minor differences between them, and also when the nucleophile is the anion of 2-mercaptoethanol. It is suggested that there is a change in the mode of transition-state binding of the esters from aryl group inclusion (**3**‡) for the short esters to acyl-group inclusion (**4**‡) when the acyl chain is lengthened beyond C_6.

The effects of cyclodextrins[1] (CDs) on the cleavage of esters in basic aqueous solution have been studied extensively.[1–4] In general, aryl esters react by acyl transfer to an ionized secondary hydroxy group of the CD, resulting in the formation of an acylated CD. For many *meta*-substituted phenyl acetates, reacting with α- and β-CD, cleavage is strongly accelerated because these esters bind to the CDs in such a way that the ester carbonyl is close to the nucleophilic site on the CD. By contrast, the reaction of *para*-substituted isomers is accelerated more modestly because they bind to CDs in a less reactive geometry.[2–4] Furthermore, there is evidence that the *para*-isomers come out of the CD cavity as the reaction takes place,[3] so that other species can occupy the CD cavity during the acyl transfer.[5]

The ease of reaction of aryl alkanoates with CDs depends on the chain length of the ester, the CD, and the position of the substituent on the phenyl group.[6–9] All but the shortest *m*- and *p*-nitrophenyl esters bind to α-CD, β-CD and hydroxypropyl-β-cyclodextrin[1d,10] (Hp-β-CD) by their acyl chains in the initial state but not necessarily in the transition state. The *m*-nitrophenyl isomers react through transition states in which their aryl groups are bound in the CD cavity (**1**‡)[7,8] because this geometry affords more efficient cleavage.[3,4] With the *p*-nitro isomers, short-chained esters also react by aryl inclusion but longer ones react through a transition state that is stabilized by acyl group inclusion (**2**‡).[7,8] By contrast, γ-CD, which has a wider cavity than α- or β-CD,[1] binds to *m*- and *p*-nitrophenyl alkanoates in the initial state by aryl-group inclusion but the transition state for cleavage involves little or no inclusion.[9] The basic cleavage of other types of aromatic esters (*e.g.*, ethyl benzoates and cinnamates) is generally retarded by complexation to CDs.[4]



1‡ **2**‡

(Note that the lower, narrower opening of the cyclodextrin is rimmed by primary hydroxy groups and the upper one by secondary hydroxy groups.)[1]

In contrast to the attention given to basic ester cleavage, few studies have been made of the attack of other nucleophiles on esters bound to CDs.[1–4] During studies of the cleavage of some 4(or 2)-carboxy-2(or 4)-nitrophenyl alkanoates by α-CD and β-CD we found evidence of the attack of a molecule of CD, presumably as its anion, on esters bound to another molecule of CD [eqn. (1)].[11] More recently, we have observed similar behaviour for Hp-β-CD reacting with nitrophenyl alkanoates and for the longest esters the kinetics suggested reaction within a ternary complex [ester•CD_2, as in eqn. (2)].[8] In a related vein, it has been reported that the attack of α-amino acids on *p*-nitrophenyl acetate (pNPA) is catalysed by CDs and this was attributed to reaction within a ternary complex {ester•CD•amine}.[12]

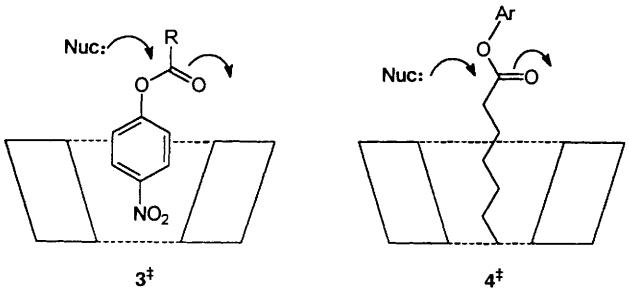
$$S + CD \rightleftharpoons S{\cdot}CD \xrightarrow{CD} \text{products} \quad (1)$$

$$S{\cdot}CD + CD \rightleftharpoons S{\cdot}CD_2 \longrightarrow \text{products} \quad (2)$$

Prompted by the findings just outlined, we are studying the effects of CDs on the attack of nucleophiles on alkanoate esters. In the first instance, we wish to find out if esters bound to CDs are more or less reactive towards 'external' nucleophiles and how their reactivities vary with the structure of the ester, the CD and the nucleophile. Later, we will study attack by nucleophiles that can also bind to CDs. Initially, we studied the reaction of trifluoroethanol (TFE), 2-mercaptoethanol, hydroxylamine and imidazole† with *p*NPA and with *p*-nitrophenyl hexanoate (*p*NPH) in the presence of three CDs, in basic solution.[13] Detailed studies with *p*NPH, TFE and three CDs established the form of the kinetics, and showed that the free and CD-bound esters have fairly similar reactivities, implying that the esters are bound in such a way that their carbonyl groups are reasonably accessible to 'external' nucleophiles. However, the studies could not resolve an important question: what is the mode of binding of the ester during the reaction with the external nucleophile?

† Reasons for choosing these four nucleophiles have been given earlier.[13]

Conceivably, the nucleophile (Nuc) could attack the ester with its aryl group included in the CD cavity, as in structure $3^{\ddagger}$, *or* with its acyl group bound in the cavity, as in $4^{\ddagger}$. The present work was undertaken specifically to address this question.



$3^{\ddagger}$ $4^{\ddagger}$

This paper reports studies of the reaction of *p*-nitrophenyl alkanoates with the anion of trifluoroethanol (TFE) in the presence of CDs; some results were also obtained with the anion of 2-mercaptoethanol (ME), as the nucleophile. The object of the work was to see how CD-mediated acyl transfer to two non-binding[13] nucleophiles respond to changing the acyl group of the ester. Based on several previous studies of chain-length effects in reactions of aliphatics in the presence of CDs,[4,6-9,11,14] a significant and systematic increase in appropriate kinetic parameters with the acyl chain length of the ester would be strong evidence that the reaction takes place with inclusion of the acyl group in the CD cavity ($4^{\ddagger}$) whereas a low sensitivity of the parameters to chain length could indicate that reaction proceeds with aryl-group inclusion ($3^{\ddagger}$).

Results

We have measured the kinetics of the cleavage of a series of *p*-nitrophenyl alkanoate esters (acetate to decanoate, C_2 to C_{10}) by trifluoroethanol (TFE) in the presence of α-CD, β-CD, or Hp-β-CD; some experiments were also carried out with mercaptoethanol (ME) and β-CD. The reaction medium was an aqueous phosphate buffer of pH 11.6 in which ME (pK_a = 9.5)[15] is almost totally ionized and TFE (pK_a = 12.4)[15] is partially ionized.

Based on previous, detailed studies of *p*-nitrophenyl hexanoate (*p*NPH) reacting with TFE and CDs,[13] our working hypothesis was composed of the four processes set out in eqns. (3)–(7). These are: hydrolysis of the ester (S) in the basic medium (3); ester cleavage through an ester•CD complex (4); reaction of the ester with the nucleophile (Nuc) (5); and reaction of the ester•CD complex with Nuc (6). With these four reactions

$$S \xrightarrow{k_u} \text{products} \quad (3)$$

$$S + CD \underset{K_S}{\rightleftharpoons} S{\cdot}CD \xrightarrow{k_c} \text{products} \quad (4)$$

$$S + Nuc \xrightarrow{k_N} \text{products} \quad (5)$$

$$S{\cdot}CD + Nuc \xrightarrow{k_{cN}} \text{products} \quad (6)$$

$$k_{obs} = \frac{(k_u K_S + k_c[CD]) + (k_N K_S + k_{cN}[CD])[Nuc]}{(K_S + [CD])} \quad (7)$$

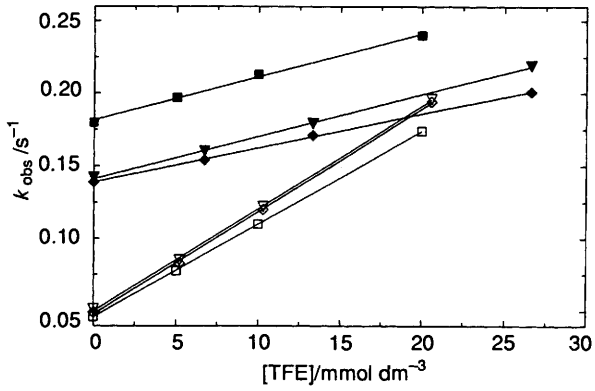


Fig. 1 Rate constants for the reaction of *p*-nitrophenyl alkanoates with TFE at pH 11.6. The straight lines are those calculated from least-squares analyses. The empty symbols (□, C_4; ▽, C_5; ◇, C_6) are for reaction in the absence of a CD; the slopes of their lines provide values of k_N. The filled symbols (■, C_4; ▼, C_5; ◆, C_6) are for reaction in the presence of 10 mmol dm^{-3} β-CD; the slopes of their lines are $(k_N K_S + k_{cN}[CD])/(K_S + [CD])$—see the text.

taking place, the expected dependence of k_{obs} on [Nuc] and [CD] is as given in eqn. (7).*

By measuring k_{obs} at various levels of [CD] and [Nuc], and analysing the results by multiple linear regression it was shown that eqn. (7) gives an excellent description of the data for *p*NPH reacting with TFE and α-CD, β-CD, or Hp-β-CD.[13] Thereafter, a simpler procedure requiring fewer measurements was adopted for other esters and nucleophiles. This procedure, which was used in the present work, entails two series of experiments with varying [Nuc]: one at zero CD and the other with a high [CD], such that most of the ester is bound to the CD. In the absence of CD, $k_{obs} = k_u + k_N[Nuc]$, and k_N is simply the slope of k_{obs} *vs.* [Nuc]. With CD present, the full form of eqn. (7) must be employed and the slope of the linear plot of k_{obs} *vs.* [Nuc] is $(k_N K_S + k_{cN}[CD])/(K_S + [CD])$. From this slope, and knowing k_N and K_S, one can estimate k_{cN}. Examples of linear plots of the observed data for three of the esters reacting with TFE in the presence and absence of β-CD are shown in Fig. 1. From their slopes the desired values of k_N and k_{cN} were determined, as just described.

Table 1 contains rate constants k_N for TFE and ME reacting with *p*-nitrophenyl alkanoates (C_2 to C_{10}) at pH 11.6 in the

Table 1 Rate constants for the cleavage of *p*-nitrophenyl alkanoates by trifluoroethanol (TFE) and mercaptoethanol (ME)[a]

	k_N/dm^3 mol^{-1} s^{-1}	
Acyl chain	TFE	ME
C_2	12.7 ± 0.1	12.5 ± 0.1
C_3	11.4 ± 0.3	
C_4	6.38 ± 0.02	8.56 ± 0.21
C_5	7.02 ± 0.09	
C_6	7.06 ± 0.11	8.53 ± 0.09
C_7	7.39 ± 0.12	
C_8	7.22 ± 0.42	6.02 ± 0.07
C_9	5.14 ± 0.03	
C_{10}	8.94 ± 0.75	9.08 ± 0.47

[a] At 25 °C, in a 0.2 mol dm^{-3} phosphate buffer of pH 11.60. At this pH, mercaptoethanol is >99.2% ionized (pK_a = 9.5)[15] so that k_N effectively refers to the anion of ME. For TFE the pK_a is 12.4,[15] so the actual rate constants for reaction of the TFE anion with the alkanoate esters would be about 6.3 times larger than k_N.

* Eqn. (7) was derived assuming that [S•CD] < $[S]_0 \ll [CD]_0$, as was the case in all experiments involving CDs.

Table 2 Dissociation constants of complexes formed between *p*-nitrophenyl alkanoate esters and cyclodextrins[a]

Acyl chain	K_S/mmol dm^{-3} α-CD	β-CD	Hp-β-CD
C_2	10	7.9[b]	8.2
C_3	7.4[c]	5.2	5.1
C_4	5.0	2.7	2.7
C_5	3.4	2.0	1.9
C_6	2.9	1.3	1.6
C_7	1.8[d]	0.79[e]	0.79
C_8	0.98[f]	0.50[e]	0.50
C_9	0.91[d]	0.39[e]	0.39
C_{10}	0.65[d]	0.16[e]	0.16
C_{12}	0.37[f]		

[a] In aqueous solutions, at 25 °C. Except where noted otherwise, the values are taken from the literature as follows: α-CD and β-CD, ref. 7; Hp-β-CD, refs. 8 and 16. [b] Ref. 5(*b*). [c] Redetermined in this study—see the Experimental section. [d] Interpolated using the correlation equation: $pK_S = 0.15n + 1.7$ ($r = 0.993$), based on the pK_S values for $n = 2, 3, 4, 5, 6, 8$ and 12.[7] [e] Assumed to be the same as for Hp-β-CD (see the text).[16] [f] Taken from ref. 6.

absence of CDs, derived from linear plots of k_{obs} *vs.* [Nuc]. Extraction of analogous values of k_{cN} from k_{obs} *vs.* [Nuc] data, as outlined above, requires values of K_S for binding of the esters to the CDs. Most of the required values were available from previous studies of the esters reacting with the CDs;[6-8] the remaining values were estimated as follows. For α-CD, they were interpolated using the linear correlation[4,7,8] of pK_S (= $-\log K_S$) with *n*, the acyl chain length.* The missing values for β-CD were taken to be the same as those for Hp-β-CD, since we have recently shown that the values of K_S for many alkyl-bearing derivatives, including nitrophenyl alkanoate esters, are virtually the same for Hp-β-CD and β-CD.[16] The K_S values used in data analysis are given in Table 2, along with their origins.

Using the approach based on eqn. (7), we have analysed kinetic data for the cleavage of *p*-nitrophenyl alkanoates by TFE and ME, reacting in the presence of CDs. Table 3 contains values of k_{cN} (and derived quantities) obtained for the reaction of TFE with the esters C_2 to C_{10} in the presence of α-CD, β-CD, and Hp-β-CD. Table 4 contains analogous constants for reaction of some of the esters with the anion $HOCH_2CH_2S^-$ in the presence of β-CD.

Discussion

The rate constants for reaction of the unbound esters with TFE and ME (k_N, Table 1) are very much as anticipated from earlier studies of nucleophilic attack on esters.[6,7,13,15] For example, the reactivities of *p*-nitrophenyl alkanoates towards hydroxide ion decrease from C_2 to C_4 by about a factor of 2, after which they remain essentially constant,[6,7] as long as the effects of substrate aggregation are minimized.[17] This same trend is seen in the values of k_N for both the TFE and ME anions acting as the nucleophiles,† meaning that beyond the propionate ester the steric effects of the *n*-acyl chains on nucleophilic attack are invariant.

The rate constants for reaction of the CD-bound esters (k_{cN}, Tables 3 and 4) do not vary greatly with ester chain length but they show more variations than values of k_N. In general, $k_{cN} < k_N$, indicating that binding the esters to CDs reduces their reactivities towards the anions of TFE and ME. However, the differences between k_{cN} and k_N are small, as found earlier for the C_2 and C_6 esters reacting with imidazole and hydroxylamine,[13] so that the CD-bound and free esters have quite similar reactivities towards the nucleophiles studied. As before,[13] we take this to mean that the esters can bind to CDs such that their carbonyl groups are exposed to the bulk medium and accessible to external nucleophiles.

Our approach to probing the mode of binding of the esters in the transition state for CD-mediated nucleophilic attack is based on the variation of kinetic parameters with the structure

Table 3 Constants for the cleavage of *p*-nitrophenyl alkanoates by trifluoroethanol (TFE) in the presence of cyclodextrins[a]

Acyl chain	k_{cN}/dm^3 mol^{-1} s^{-1}	k_{cN}/k_N	k_3/dm^6 mol^{-2} s^{-1}	K_{TS}/mmol dm^{-3}
α-Cyclodextrin				
C_2	8.03 ± 0.09	0.63	800	16
C_3	5.67 ± 0.14	0.50	760	15
C_4	1.73 ± 0.06	0.27	350	18
C_5	1.56 ± 0.02	0.22	460	15
C_6	1.88 ± 0.06	0.27	650	11
C_7	1.46 ± 0.06	0.20	810	9.1
C_8	1.67 ± 0.05	0.23	1 700	4.2
C_9	2.57 ± 0.11	0.50	2 800	1.8
C_{10}	1.79 ± 0.01	0.20	2 800	3.3
β-Cyclodextrin				
C_2	10.4 ± 0.1	0.82	1 300	9.7
C_3	6.28 ± 0.24	0.55	1 200	9.4
C_4	2.09 ± 0.08	0.33	770	8.2
C_5	2.05 ± 0.04	0.29	1 000	6.9
C_6	1.71 ± 0.02	0.24	1 300	5.4
C_7	2.26 ± 0.33	0.31	2 900	2.6
C_8	4.18 ± 1.25	0.58	8 400	0.86
C_9	4.11 ± 0.13	0.80	11 000	0.49
C_{10}	7.73 ± 2.13	0.86	49 000	0.18
Hydroxypropyl-β-cyclodextrin				
C_2	7.28 ± 0.18	0.57	890	14
C_3	4.52 ± 0.12	0.40	900	13
C_4	2.25 ± 0.03	0.35	840	7.6
C_5	1.18 ± 0.05	0.17	610	12
C_6	1.28 ± 0.01	0.18	805	8.8
C_7	1.58 ± 0.02	0.21	2 000	3.7
C_8	1.83 ± 0.04	0.25	3 700	2.0
C_9	1.86 ± 0.10	0.36	4 800	1.1
C_{10}	3.02 ± 0.05	0.34	19 000	0.47

[a] At 25 °C, in a 0.2 mol dm^{-3} phosphate buffer of pH 11.60. The corresponding values of k_N are given in Table 1. The third-order rate constant, $k_3 = k_{cN}/K_S$, where K_S is taken from Table 2. The apparent dissociation constant K_{TS} is defined in eqn. (9).

Table 4 Constants for the cleavage of *p*-nitrophenyl alkanoates by mercaptoethanol in the presence of β-cyclodextrin[a]

Acyl chain	k_{cN}/dm^3 mol^{-1} s^{-1}	k_{cN}/k_N	k_3/dm^6 mol^{-2} s^{-1}	K_{TS}/mmol dm^{-3}
C_2	9.78 ± 0.52	0.78	1 200	10
C_4	3.86 ± 0.05	0.45	1 400	6.0
C_6	2.06 ± 0.01	0.24	1 600	5.4
C_8	2.67 ± 0.01	0.44	6 400	1.1
C_{10}	15.6 ± 0.9	1.7	98 000	0.093

[a] At 25 °C, in a 0.2 mol dm^{-3} phosphate buffer of pH 11.60. The corresponding values of k_N are given in Table 1. The third-order rate constant, $k_3 = k_{cN}/K_S$, where K_S is taken from Table 2. The apparent dissociation constant K_{TS} is defined in eqn. (9).

* Since hydrophobicity and other properties of *n*-alkyl chains increase linearly with their lengths, such correlations with chain length are effectively liner free energy relationships (LFERs).[3,4,7-9]

† Admittedly, there is some dispersion in the data for the C_9 and C_{10} esters. This may result from the poorer quality of the data for these substrates due to the necessity of using very low concentrations of them.

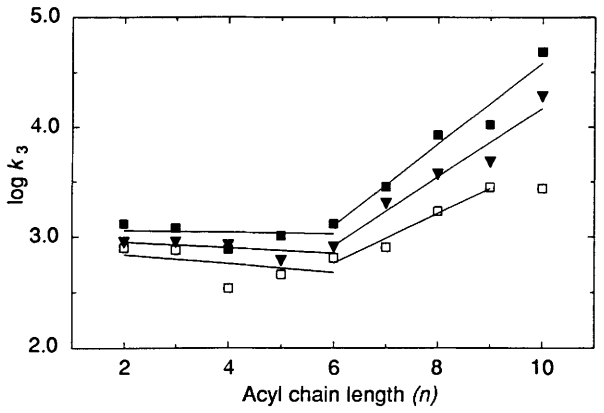


Fig. 2 Chain-length dependence of the third-order rate constants (k_3) for the reaction of *p*-nitrophenyl alkanoates with TFE and cyclodextrins: □, α-CD; ▼, Hp-β-CD; ■, β-CD. The straight lines are from least-squares analyses of the data in two domains: C_2 to C_6; C_6 and above. The slopes of the lines are discussed in the text.

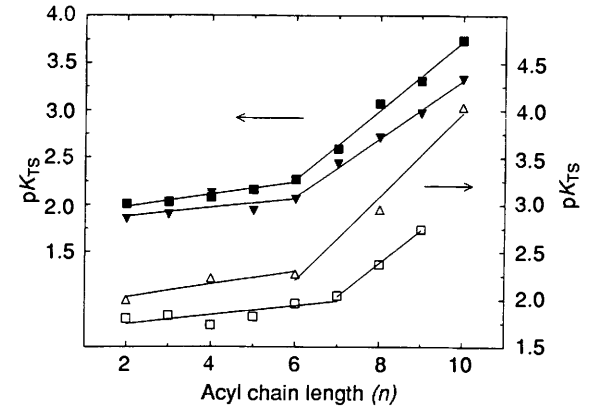


Fig. 3 Chain-length dependence of transition-state stabilization (pK_{TS}) for the reaction of *p*-nitrophenyl alkanoates with CDs and TFE or ME. The symbols are: □, α-CD + TFE; △, β-CD + Me; ▼, Hp-β-CD + TFE; ■, β-CD + TFE. Note that the left and right *y*-scales are purposely offset, for clarity. Otherwise, the data points for β-CD and ME would lie almost on top of those for β-CD + TFE. The point for the C_{10} ester + TFE + α-CD has been omitted because it appears to be anomalous (*cf.*, Fig. 2). The straight lines are from least-squares analyses of the data in two domains: C_2 to C_6; C_6 and above. The slopes of the lines are discussed in the text.

of the esters.[4,7–9,11] In particular, we will look at the chain length dependence of the reactivity ratios k_{cN}/k_N, the third-order rate constants, k_3 [eqn. (8)] and the 'dissociation constants' of the transition states, K_{TS} [eqn. (9)]. The rate constants k_3 are for the mutual reactivity of the ester, CD and nucleophile; they are equal to k_{cN}/K_S by virtue of the kinetic equivalence of the processes in eqns. (6) and (8).

$$S + CD + Nuc \xrightarrow{k_3} \text{products} \qquad (8)$$

The pseudo-equilibrium constants K_{TS} are obtained using an approach based on transition-state theory.[18] Variations of K_{TS}, or better $pK_{TS} = -\log K_{TS}$, with structure are useful probes of transition-state binding.[4] For the present purposes, we define K_{TS} [eqn. (9)] as the apparent dissociation constant of the

$$K_{TS} = \frac{[TS][CD]}{[TS{\cdot}CD]} = \frac{k_N K_S}{k_{cN}} = \frac{k_N}{k_3} \qquad (9)$$

transition state of the CD-mediated reaction [eqn. (6) or eqn. (8)], symbolized by TS·CD, into the transition state (TS) of the normal reaction [eqn. (5)] and the CD.

The reactivity ratios k_{cN}/k_N do not vary appreciably with chain length but they generally decrease for the C_2 to C_6 esters and then rise again from C_6 to C_{10}. Since k_N values are fairly insensitive to the ester chain (Table 1), this pattern results mainly from variations in k_{cN} (Tables 3 and 4). In contrast to k_{cN} or k_N, the values of the third-order rate constants k_3 for the reaction of the esters with TFE and the CDs show a wide variation, ranging from 350 to 49 000 $dm^6\ mol^{-2}\ s^{-1}$ (Table 3). Moreover, they show a distinct pattern: k_3 values are relatively invariant for the C_2 to C_6 esters but they increase 30–40 fold from C_6 to C_{10}. Similarly, values of K_{TS} do not vary much for the five shortest esters but for the longer ones they decrease appreciably. These well-defined trends are clearly shown by the plots of log k_3 *vs.* chain length (*n*) in Fig. 2 and by the plots of pK_{TS} *vs.* *n* in Fig. 3.

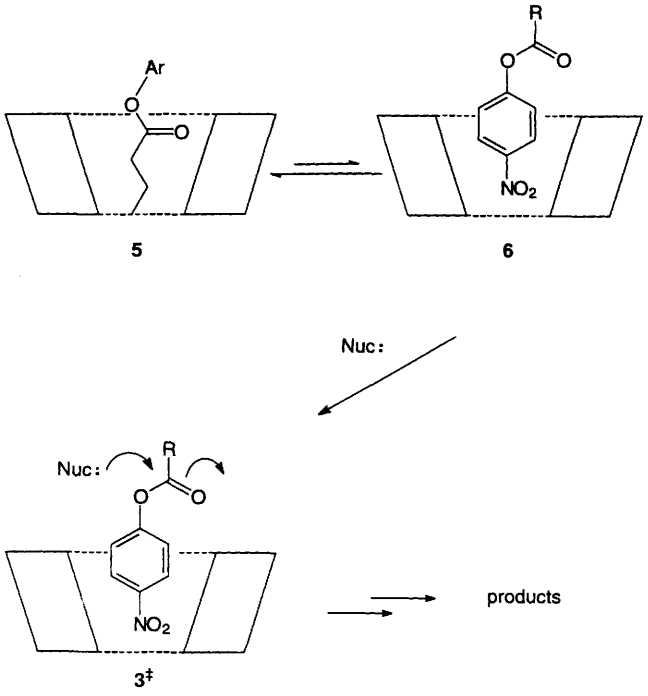
The strength of substrate binding of the aryl alkanoates to α-CD, β-CD and Hp-β-CD varies monotonically with their acyl chain length.[4,7,8,11] Plots of pK_S *vs.* *n*, which are treated as linear free energy relationships (LFERs),* have slopes of about +0.2, providing excellent evidence that, except for the acetate, the esters bind to CDs by acyl-group inclusion.[7,8] In stark contrast to these simple, linear correlations for substrate binding, the variations in the plots of log k_3 against *n* (Fig. 2) are all *biphasic*, with two distinct linear portions: for $n = 2$ to 6 the slopes are near zero (−0.04 to −0.01) but from $n = 6$ to 10 they are much steeper (+0.22 to +0.37). The plots of pK_{TS} *vs.* *n* (Fig. 3) are also distinctly biphasic, with gentle slopes (+0.05 to +0.07) for $n = 2$ to 6 and steep slopes (+0.31 to +0.44) for $n = 6$ to 10.

From the biphasic plots in Fig. 2 and Fig. 3, we conclude that the nucleophiles react with short esters ($< C_6$) which have their *p*-nitrophenyl groups bound in the CD cavity, as in **3**‡, and that reaction of the longer esters ($> C_6$) takes place with acyl-chain inclusion, as shown in **4**‡. Previously, we observed similar biphasic behaviour for reaction of the same *p*-nitrophenyl alkanoates with Hp-β-CD, with the breakpoint also at C_6, and we attributed it to acyl transfer taking place through aryl inclusion (**1**‡) for the shorter esters and through acyl-group inclusion (**2**‡) for the longer ones.[8]

Another noteworthy feature of the data in Tables 3 and 4 is that K_{TS} values for the CD-mediated acyl transfer to the anions of ME and TFE are essentially identical. Earlier, we found that K_{TS} values for the CD-mediated reactions of *p*NPA and *p*NPH with NH_2OH and with imidazole are almost the same, also.[13] Taken together, these observations mean that the strength of the transition-state binding to the CD is virtually independent of the nucleophile, which is consistent with our picture of the acyl transfer as taking place outside of the CD cavity, in a largely aqueous environment (through **3**‡ or **4**‡), and that the CD simply provides a binding site for the aryl group or acyl group of the ester.

It is appropriate to ask why short *p*-nitrophenyl alkanoates react with nucleophiles through aryl inclusion (**3**‡) but longer esters react with acyl inclusion (**4**‡). We propose that for those short esters which are bound by their acyl chains[6–8] the principal {ester·CD} complex is not sufficiently reactive towards external nucleophiles because the ester carbonyl is relatively buried in the CD cavity (**5**). Consequently, this complex must undergo rearrangement to a less stable, aryl-bound form (**6**) which has the carbonyl group more exposed to external attack and which reacts through **3**‡. Not until the alkanoate chain has six or more carbons does the carbonyl group in the dominant {ester·CD} complex sit far enough out of the CD cavity for facile reaction with nucleophiles as in **4**‡.

* Since hydrophobicity and other properties of *n*-alkyl chains increase linearly with their lengths, such correlations with chain length are effectively linear free energy relationships (LFERs).[3,4,7–9]



If we suppose that the shorter esters react through a less stable, aryl-bound {ester•CD} complex, as in $\mathbf{5} \rightleftharpoons \mathbf{6}$ + Nuc $\longrightarrow \mathbf{3}^{\ddagger} \longrightarrow$ products [eqn. (10)], we can estimate rate

$$S + CD \underset{K'_S}{\rightleftharpoons} S{\cdot}CD' \xrightarrow[Nuc]{k'_{cN}} \text{products} \qquad (10)$$

constants (k'_{cN}) for reaction with the nucleophile from the previously obtained values of k_3 ($= k'_{cN}/K'_S$), using an assumed value of K'_S for aryl-group binding. Assuming that $K'_S = 10$ mmol dm^{-3} (*cf.*, *p*NPA, Table 2), the values of k'_{cN} (in dm^3 mol^{-1} s^{-1}) for reaction with TFE fall within very narrow ranges: 3.5–8.1 (α-CD); 5.0–7.4 (Hp-β-CD); 6.2–10.4 (β-CD). These values, which correspond to reactivity ratios k'_{cN}/k_N of 0.55–1.5, and which show no systematic dependence on acyl-chain length, are perfectly consistent with reaction through the aryl-bound transition state, $\mathbf{3}^{\ddagger}$.

The results for CD-mediated nucleophilic attack are not particularly different for the three CDs (Table 3, Fig. 2 and Fig. 3) but they consistently show an order of transition-state stabilization (pK_{TS}) of: β-CD > Hp-β-CD > α-CD.* This same order is found in the results for cleavage of *p*-nitrophenyl alkanoates by the CDs,[7,8] suggesting that the similar features of binding are operative in the transition states of two reactions, both for those occurring with aryl inclusion ($\mathbf{1}^{\ddagger}$ and $\mathbf{3}^{\ddagger}$) and those with acyl-group inclusion ($\mathbf{2}^{\ddagger}$ and $\mathbf{4}^{\ddagger}$).

Conclusions

The reactivites of *p*-nitrophenyl alkanoates towards nucleophilic attack by the anions of trifluoroethanol and 2-mercaptoethanol are generally reduced when they are bound to cyclodextrins (α-CD, β-CD and Hp-β-CD) but the extent varies systematically with the acyl chain length (n) of the ester. Third-order rate constants for reaction of the ester with TFE and the CDs vary in a biphasic manner with n, as do apparent dissociation constants that are indicative of transition-state stabilization. It is proposed that for short esters (C_2 to C_6), nucleophilic attack takes place with the *p*-nitrophenyl group of the ester included in the CD cavity ($\mathbf{3}^{\ddagger}$) whereas for the longer esters (C_7 to C_{10}) reaction occurs through a transition state having acyl inclusion ($\mathbf{4}^{\ddagger}$). This dichotomy arises because acyl-bound esters with short chains (*e.g.*, **5**) have carbonyl groups that are not easily accessible to reagents outside the CD cavity. As a result, the acyl-bound form must rearrange to a aryl-bound form ($\mathbf{5} \longrightarrow \mathbf{6}$) whose carbonyl group is more reactive because it is exposed to external, nucleophilic attack.

Experimental

The cyclodextrins, TFE and ME were purchased from Aldrich and used as supplied. The 'hydroxypropyl-β-cyclodextrin' had an average molecular weight of 1500, corresponding to alkylation of six of the seven primary hydroxy groups of β-CD by 2-hydroxypropyl groups.[10] Most of the esters were obtained from Sigma except for the C_7 and C_9 esters which were synthesized by a DCC method, as previously.[8]

Kinetics procedures were basically the same as in our previous paper.[13] Reactions were carried out by mixing equal volumes of the nucleophile with the alkanoate ester in a stopped-flow apparatus. For the experiments with 10 mmol dm^{-3} of α-CD or Hp-β-CD, one syringe contained the basic buffer and nucleophile while the other contained the ester and 20 mmol dm^{-3} of the CD. For β-CD, which is less soluble in water, both syringes contained 10 mmol dm^{-3}. The phosphate buffer of pH 11.60 was 0.2 mol dm^{-3}, after mixing. The substrate concentrations used in the reactions were between 5 and 50 μmol dm^{-3}, according to the solubility of the esters in water.

The kinetics of ester cleavage were followed by monitoring the first-order appearance of the *p*-nitrophenolate ion at 405 nm, using an Applied Photophysics SX17MV Stopped-flow Spectrophotometer, as described previously.[13] The temperature of the observation cell of the apparatus was maintained at 25.0 ± 0.1 °C. For the long esters, which must be studied at very low concentrations, 5–10 absorbance traces were computer-averaged before estimation of k_{obs} by non-linear least-squares fitting.

Use of the analysis based on eqn. (7), as outlined in the main text, requires known values of K_S for binding between the esters and the CDs. Such values were available from a recent study for all the esters and Hp-β-CD,[8] and from earlier studies[6,7] for most of the esters binding to α-CD and β-CD.

Kinetic parameters for the cleavage of *p*-nitrophenyl propionate by α-CD were redetermined because earlier values[7] appeared to be anomalous. For reaction in phosphate buffer at pH 11.6, we found $k_u = 0.0938$ s^{-1} and by non-linear fitting of a saturation curve[7,8] to the kinetic data we obtained $k_c = 0.163 \pm 0.005$ s^{-1} and $K_S = 7.42 \pm 0.92$ mmol dm^{-3}.

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* It is intriguing that the transition-state stabilization by Hp-β-CD is less than that by β-CD (see pK_{TS} values in Fig. 3). One possibility is that the CD-bound ester sits slightly deeper in the cavity of Hp-β-CD than in the β-CD cavity, even though the pK_S values for these two CDs are essentially identical,[8,16] thereby making attack on the carbonyl group by the external TFE anion somewhat more difficult.

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