The cleavage of 1- and 2-naphthyl acetates by cyclodextrins in basic aqueous solution

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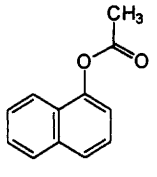
The reactions of 1- and 2-naphthyl acetate (1-NA and 2-NA) with four cyclodextrins (CDs): α-CD, β-CD, γ-CD, and 'hydroxypropyl-β-CD' (Hp-β-CD), in basic aqueous solution, all show saturation kinetics. Even though the strength of substrate binding varies appreciably, the limiting accelerations at high [CD] are all relatively modest (3 to 30-fold). The effects on the two isomeric esters are generally similar but there are significant differences between the CDs. These differences are discussed in terms of the relative importance of transition-state and initial-state binding, and in relation to structural variations in the four cyclodextrins. Except for one case, the second-order rate constants (k_2) for the reactions of 1-NA and 2-NA with the CDs are appreciably greater than those for reaction with trifluoroethanol (TFE), as expected for stabilization of the transition state by inclusion of part of the ester in the CD cavity. For 2-NA reacting with α-CD, k_2 is virtually the same as that for reaction with TFE, suggesting that inclusion is not a significant factor in this particular case. Consistent with this suggestion, the cleavage of 2-NA by α-CD is not competitively inhibited by alcohols, it is mediated by them. The cleavage of 1-NA by β-CD can also be mediated by alcohols and by alkanesulfonate ions, but the analogous reaction of 2-NA is not as susceptible.

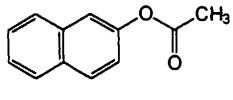
Cyclodextrins (CDs) are cyclic oligosaccharides that are composed of glucose units joined together in a toroidal fashion.[1] As a result, each CD has a cavity with which it may form inclusion compounds and CDs can act as hosts towards a vast array of organic and inorganic guests.[1,2] The three main CDs, designated as α-CD, β-CD, and γ-CD, contain 6, 7 and 8 glucose units, respectively, so that the widths of their cavities increase in a regular manner. Not surprisingly, the abilities of these three CDs to form inclusion compounds with molecules of different shapes and sizes vary in accordance with their dimensions. Roughly speaking, the size of α-CD is appropriate for inclusion of a benzene ring, β-CD can accommodate a naphthalene ring, and γ-CD can include anthracene.[3] Thus, it is to be expected that the three CDs can have varying effects on reactivity because of their different sizes, and depending on the involvement (or otherwise) of their cavities in the reaction in question. Such is the case with ester cleavage.

The cleavage of substituted phenyl acetates by CDs in basic aqueous solution has been studied by many researchers,[4-7] including several in this laboratory.[8-12] In general, *meta*-substituted isomers are cleaved much more efficiently by α-CD than are their *para* isomers. This difference arises because the *meta* isomers bind to the CD in a way that is well suited for the acyl transfer reaction, meaning that inclusion of a *meta* substituent makes a positive contribution to transition-state stabilization.[5] By contrast, a *para* substituent does not help transition-state formation and it may even be a hindrance.[7d,11] For the reaction of phenyl acetates with β-CD, whose cavity is wider, and in which the esters fit less tightly, the difference in reactivity between the isomers is less marked but it is still appreciable. However, for the reaction of phenyl acetates with γ-CD, the even wider cavity leads to a very loose fit of each ester so that there is hardly any difference in the behaviour of *meta* and *para* isomers.[6a,12b]

The present paper deals with the basic cleavage of 1-naphthyl acetate (1-NA) and 2-naphthyl acetate (2-NA) by cyclodextrins. In the first instance, we wished to find out if these two positional isomers differ significantly in their reactivity towards CDs (in the way that *m*- and *p*-substituted phenyl acetates do with α-CD and β-CD). Judging from previous work on naphthalene derivatives,[1,3a,13] the isomers 1-NA and 2-NA may bind to the CDs in different orientations which could affect their reactivities in the cleavage reaction. Secondly, we were interested to see how differences in the kinetic parameters for the cleavage of 1-NA and 2-NA vary with the size and nature of the CD. Significant variations might provide insight into transition-state and initial-state binding, and into any differences between them.[5] Therefore, we have studied the reactions of 1-NA and 2-NA with four cyclodextrins: α-CD, β-CD, γ-CD, and a modified CD, 'hydroxypropyl-β-cyclodextrin' (Hp-β-CD). In this last derivative, essentially all of the seven primary hydroxy groups of β-CD have been alkylated with 2-hydroxypropyl groups.[1b,1c,14] Conceivably, this modification may simply extend the depth of the cavity of β-CD or, if the hydroxypropyl groups are turned in towards the central axis of the CD cavity, they may close off the bottom of the cavity so as to provide an 'intrusive floor'.[15] Either way, the binding characteristics of Hp-β-CD may be subtly altered relative to β-CD, even though studies of the binding of many simple aliphatic derivatives indicate that there is little difference in the strength of binding.[16]



1-NA



2-NA

Results

We have measured the kinetics of cleavage of 1-NA and 2-NA by α-CD, β-CD, γ-CD and Hp-β-CD, in an aqueous phosphate buffer of pH 11.6. Pseudo-first-order rate constants (k_{obs}) were obtained over a range of CD concentrations and in all cases the reactions showed simple saturation kinetics.[1a,5-8] This type of behaviour is consistent with reaction in the medium [eqn. (1)] and reaction through a substrate•CD complex [eqn. (2)] or its kinetic equivalent,[4,5,8] so that the variation of the observed rate constant with [CD] is given by eqn. (3).

Table 1 Constants for the basic cleavage of 1- and 2-naphthyl acetate by cyclodextrins and trifluoroethanol[a]

CD	k_u/s^{-1}	k_c/s^{-1}	k_c/k_u	K_S/mmol dm^{-3}	K_{TS}/mmol dm^{-3}	k_2/dm^3 mol^{-1} s^{-1}
(*a*) 1-Naphthyl acetate						
α-CD	0.015	0.44 ± 0.04	30	39 ± 5	1.3	12
β-CD	0.016	0.503 ± 0.003	31	6.3 ± 0.1	0.20	80
Hp-β-CD	0.015	0.072 ± 0.001	4.7	3.13 ± 0.02	0.67	23
γ-CD	0.014	0.122 ± 0.003	8.8	10.7 ± 0.6	1.2	11
TFE	0.015		—		13	1.18 ± 0.01[b]
(*b*) 2-Naphthyl acetate						
α-CD	0.022	0.068 ± 0.001	3.0	25 ± 6	8.24	2.7
β-CD	0.022	0.330 ± 0.003	15	1.32 ± 0.05	0.086	250
Hp-β-CD	0.020	0.076 ± 0.001	3.8	0.73 ± 0.03	0.19	105
γ-CD	0.023	0.69 ± 0.02	30	7.9 ± 0.6	0.26	88
TFE	0.022	—	—		11	2.00 ± 0.06[b]

[a] At 25 °C, in aqueous solution at pH 11.6. The constants K_S and k_c were obtained by fitting of eqn. (3) and the uncertainties are the standard errors from the fitting. Four examples of the data are shown in Fig. 1. The derived constants are: $k_2 = k_c/K_S$ and $K_{TS} = k_u/k_2$. [b] Trifluoroethanol does not give saturation kinetics and k_2 is simply the slope of k_{obs} against [TFE].

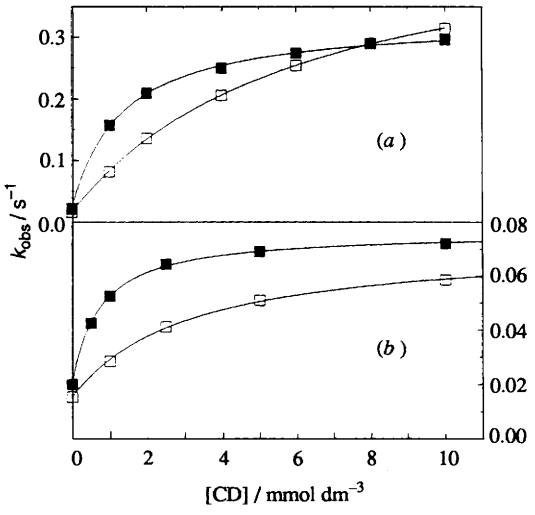


Fig. 1 Examples of saturation kinetics for the cleavage of 1- and 2-naphthyl acetates by cyclodextrins: (*a*) cleavage by β-CD; (*b*) cleavage by Hp-β-CD. The open squares (□) are for 1-NA and the filled squares (■) denote 2-NA. The curves are calculated from eqn. (3), using constants from Table 1. Note that the vertical scales in (*a*) and (*b*) are not the same. The actual data for Hp-β-CD extend out to 20 mmol dm^{-3}.

$$S \xrightarrow{k_u} \text{products} \quad (1)$$

$$S + CD \underset{K_S}{\rightleftharpoons} S{\cdot}CD \xrightarrow{k_c} \text{products} \quad (2)$$

$$k_{obs} = \frac{(k_u K_S + k_c[CD])}{(K_S + [CD])} \quad (3)$$

Some examples of the observed data are presented in Fig. 1 (*a* and *b*), together with curves calculated using eqn. (3). Fitted values of k_c and K_S for all the cases studied are given in Table 1, along with derived constants that are to be used in later discussion. Table 1 also contains the second-order rate constants for the reaction of 1-NA and 2-NA with trifluoroethanol (TFE) which were obtained for comparative purposes. Since TFE has a pK_a (12.4)[17] close to that of CDs (12.2, 12.3),[18] the nucleophilicities of the CD anions should be very similar to that of the trifluoroethoxide anion, other things being equal.

For reasons explained later in the discussion, we have also studied the reaction of 1-NA with β-CD in the presence of potential inhibitors. Under normal circumstances, an inhibitor (here, PI) binds to the CD [eqn. (4)] so that the free CD

$$PI + CD \underset{K_i}{\rightleftharpoons} PI + CD \quad (4)$$

concentration is lowered and k_{obs} is reduced in accordance with eqn. (3). Such behaviour, which is generally known as competitive inhibition,[19] is observed for the cleavage of *m*-nitrophenyl acetate (*m*NPA) by α-CD, β-CD and Hp-β-CD,[6,11,16] but many potential inhibitors (PIs) do not retard the cleavage of *p*-nitrophenyl acetate (*p*NPA) to the same extent.[11] Likewise, we have found that the cleavage of 1-NA by β-CD is not fully inhibited by various PIs; three examples of the behaviour are shown in Fig. 2(*a*).

As previously,[11] we postulate the existence of a PI-mediated process [eqn. (5)] which partially or totally overcomes the

$$PI + CD + S \underset{K_S}{\rightleftharpoons} PI + CD{\cdot}S \xrightarrow{k_a} \text{products} + PI \quad (5)$$

effects of competitive inhibition. The presence of this process requires that eqn. (3) is replaced by eqn. (6). For the purposes of

$$k_{obs} = \frac{(k_u K_S + k_c[CD] + k_a[PI][CD])}{(K_S + [CD])} \quad (6)$$

analysis we arrange eqn. (6) to eqn. (7) which requires a linear

$$k_{corr} = \{k_{obs}(K_S + [CD]) - k_u K_S\}/[CD] = k_c + k_a[PI] \quad (7)$$

dependence of k_{corr} on [PI], from whose slope the rate constant k_a is obtainable. Three examples of such linear dependence are given in Fig. 2(*b*), corresponding to the raw data in Fig. 2(*a*). The values of k_a obtained for 12 alcohols[20] and 5 alkanesulfonate ions[21] are collected in Table 2.

We have also looked at the effect of PIs on cleavage 2-NA by β-CD. For short alcohols (C_3 or C_4), a PI-mediated process was discernible but with larger alcohols, which must be used at lower concentrations, the effect is not distinguishable from competitive inhibition. By contrast, the cleavage of 2-NA by α-CD was found to be mediated by alcohols in much the same way as the cleavage of 1-NA by β-CD (Table 2).

Discussion

According to spectroscopic studies by Harata and Uedaira,[13] simple 1-naphthyl derivatives bind to β-CD in an 'equatorial'

manner (*e.g.* **1**, Scheme 1) whereas isomeric 2-naphthyl derivatives bind in an 'axial' fashion (*e.g.* **2**, Scheme 2). Binding studies of naphthalene derivatives by other workers are consistent with these views.[3a] The 'equatorial' orientation (**1**) does not appear to be particularly appropriate for reaction between the ester group of 1-NA and an ionized secondary hydroxy group: either 1-NA would have to come more or less right out of the β-CD cavity to react or, more likely, reaction would take place through an isomeric ester•CD complex in which the naphthalene ring has an 'axial' disposition (**1'**, Scheme 1). On the other hand, binding of 2-NA in an 'axial' manner (**2**) appears to be more suited to reaction, although the naphthalene ring of the ester might still need to come out of the cavity to some extent (**2'**, Scheme 2).

In subsequent discussion we will use Schemes 1 and 2 as working hypotheses and try to relate the kinetic results to them. However, one must bear in mind that the situation may be altered considerably by the smaller size of α-CD, the larger size of γ-CD, and to a lesser extent by the modified primary hydroxy groups of Hp-β-CD.

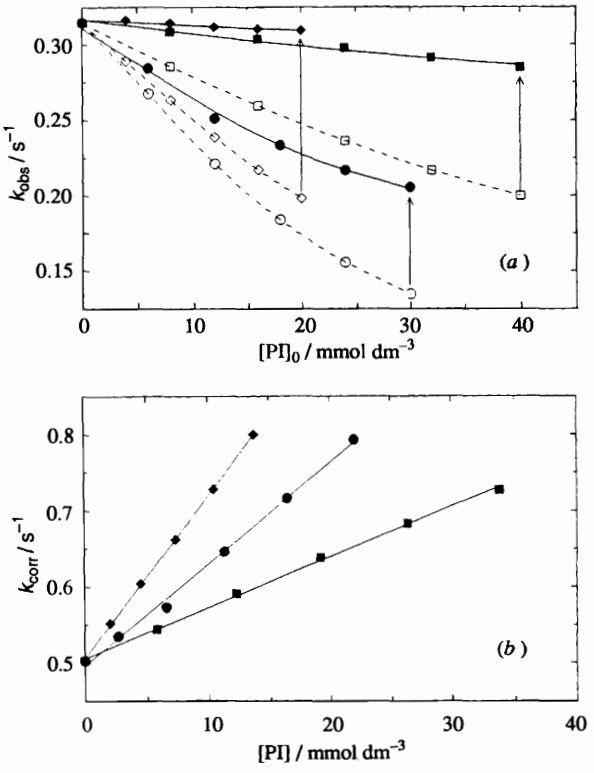
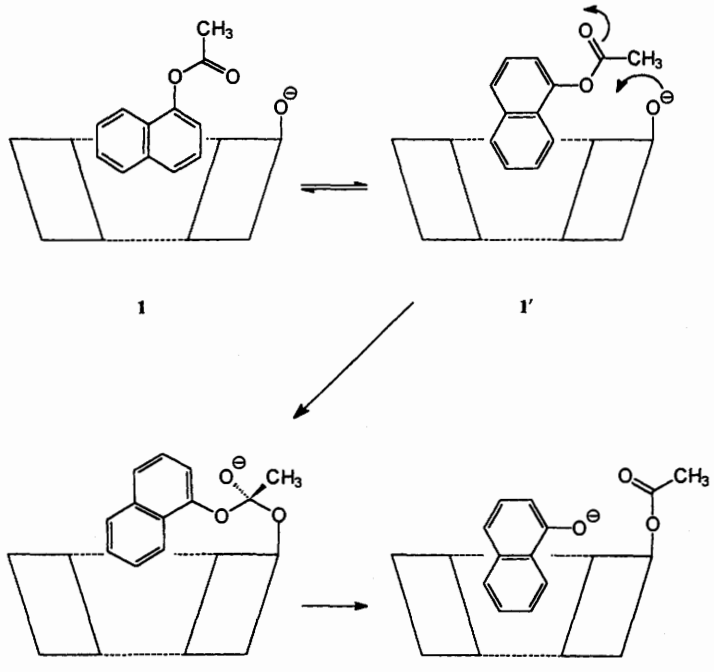


Fig. 2 Examples of the effects of potential inhibitors on the cleavage of 1-NA by β-CD. The symbols are: ■, Bu^{t}OH; ●, $HexSO_3^-$; ◆, cyclo-PentOH. (*a*) Dependence of k_{obs} on the total concentration of PI. The dashed curves (and open symbols) are those calculated for competitive inhibition while the solid curves are those calculated for PI-mediated cleavage [eqn. (6)]. (*b*) Dependence of k_{corr} on the actual concentration of PI [eqn. (7)] for the same data as in (*a*). The slopes of such plots afford the rate constants k_a given in Table 2.

Substrate binding (K_S)

For both 1-NA and 2-NA, the strength of substrate binding follows the order: Hp-β-CD > β-CD > γ-CD > α-CD (Table 1). Thus, as expected from earlier studies,[1b,3] β-CD binds both naphthyl esters better than either α-CD or γ-CD does. Presumably, α-CD binds weakly because its cavity is too small, and the naphthyl ester is more or less constrained to perch on the top.[3a] On the other hand, the cavity of γ-CD is too large for a snug fit of the naphthalene rings, so that the esters fit loosely and their binding is weaker, as a result. Relative to β-CD, Hp-β-CD binds each ester about twice as strongly, possibly because the hydroxypropyl groups on the primary side turn inwards to form an intrusive floor.[15]

Comparing the two esters, we note that 2-NA binds more strongly in all cases, particularly with β-CD and Hp-β-CD. With these two CDs, we presume that the orientation of the naphthalene ring of 2-NA is 'axial', as in structure **2**. The weaker binding of 1-NA may be associated with the 'equatorial' orientation (**1**) or it may result from 'axial' binding which is not as strong because the substituent at the 1-position does not allow the naphthalene ring to enter the CD cavity as far (**1'** in Scheme 1). For both α-CD and γ-CD the difference in the strength of binding of the two esters is small, which is reasonable if the modes of binding of 1-NA and 2-NA are similar in each case: perched on top in the case of α-CD; more deeply included in the case of γ-CD.[3a]

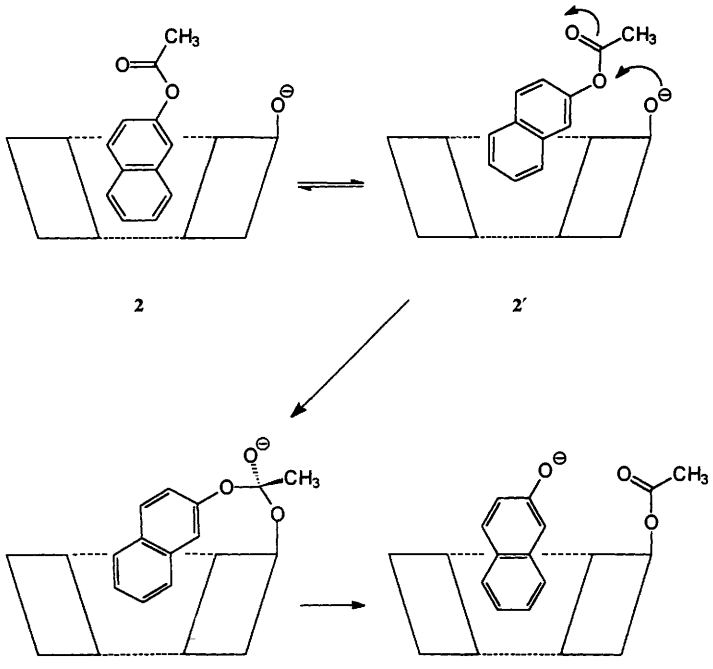


Scheme 1 Reaction of 1-naphthyl acetate with β-CD

Table 2 Constants for the effects of potential inhibitors (PIs) on the basic cleavage of 1- or 2-naphthyl acetate by α- or β-cyclodextrin[a]

PI	K_I/mmol dm^{-3}	k_a/dm^3 mol^{-1} s^{-1}	k_b/dm^3 mol^{-1} s^{-1}	K_{TS}'/mmol dm^{-3}
(*a*) Effect of alcohols on the cleavage of 1-NA by β-CD				
Et	1070	0.275	46.9	1830
Pr^n	269	0.982	42.0	510
Bu^n	60.3	3.31	31.7	150
Pen^n	15.9	5.66	14.3	89
Hex^n	4.57	12.4	9.0	41
2-Pr	263	1.08	45.4	460
2-Bu	64.6	2.92	30.0	172
2-Pen	32.4	3.35	17.2	150
2-Hex	10.5	5.46	9.1	92
Bu^t	20.9	6.67	22.1	75
cycloPent	8.32	21.3	28.2	24
cycloHex	1.66	51.4	13.6	9.8
(*b*) Effect of alkanesulfonate ions on the cleavage of 1-NA by β-CD				
C_4	89.1	1.86	24.6	270
C_5	16.6	6.20	16.4	81.1
C_6	5.62	13.3	11.9	37.8
C_7	2.29	17.5	6.35	28.8
C_8	0.977	31.3	4.87	16.1
(*c*) Effect of alcohols on the cleavage of 2-NA by α-CD				
Et	177	0.332	2.35	205
Pr^n	42.7	0.559	0.952	121
Bu^n	11.2	3.31	1.48	20.5
Pen^n	3.09	7.93	0.978	8.56
Hex^n	1.12	16.8	0.752	4.04
Hept^n	0.437	48.0	0.836	1.41

[a] At 25 °C, in an aqueous phosphate buffer (pH 11.6) containing 10 mmol dm^{-3} β-CD. The dissociation constants of the PI•CD complexes (K_I) are taken from the literature[7d,20,21] and previous work.[11,16] Values of k_a are the slopes of k_{corr} against [PI], based on eqn. (7), k_b values are calculated from k_aK_I/K_S, and $K_{TS}' = k_c/k_a$.



Scheme 2 Reaction of 2-naphthyl acetate with β-CD

Rate acceleration (k_c/k_u)

This ratio measures the maximal acceleration of the reaction at saturating levels of the CD. Esterolysis of 1-NA and 2-NA is accelerated by all four CDs, but the ratio varies only from 3 to 30 (Table 1). For comparison, ratios of up to 360 have been found for *m*-substituted phenyl acetates reacting with α- and β-CD, and much lower and higher values for other types of esters.[5] Interestingly, three different ester/CD combinations (1-NA/α-CD, 1-NA/β-CD, 2-NA/γ-CD) give the largest ratio of 30. As discussed later, this situation basically arises because of parallelism between transition-state binding and substrate binding.

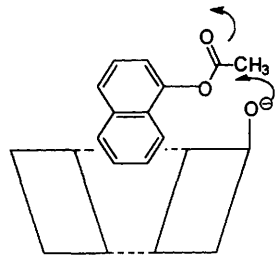
Substrate selectivity (k_2)

The second-order rate constants k_2 [$=k_c/K_S$, eqn. (2)] measure the reactivity of ester with CDs, under non-saturating

conditions, and variations of k_2 with the structure of the ester or the CD can provide clues to the mode of binding of the esters to CDs in the transition state of the cleavage reaction.[4-10] For 1-NA, the order of reactivity is β-CD > Hp-β-CD > α-CD ~ γ-CD > TFE, whereas for 2-NA the order is β-CD > Hp-β-CD > γ-CD > α-CD ~ TFE (k_2, Table 1). The difference between these orders is due primarily to the placement of α-CD, which is the only CD that reacts more rapidly with 1-NA than with 2-NA. For α-CD and 2-NA, the value of k_2 is almost equal to that for the reaction of TFE with 2-NA, meaning that the anion of α-CD has essentially the same nucleophilicity towards 2-NA as a simple oxyanion of the same basicity. Thus, for 2-NA reacting with α-CD, it seems that inclusion in the CD cavity does not contribute significantly to stabilization of the cleavage transition state. By contrast, all the other values of k_2 for the esters and CDs are substantially larger (up to 125 times) than the values for TFE (Table 1), indicating that inclusion in the CD is a contributing factor in these other cases.

With the sole exception of α-CD, 2-NA reacts more readily with the CDs than 1-NA does (Table 1). In part, this superiority simply reflects the electrophilicity of 2-NA which is cleaved about twice as fast by simple nucleophiles† but since the factors are greater than two there is greater transition-state stabilization for the reaction of 2-NA. This additional stabilization must be related to superior transition-state binding and it is most likely due to the differences in geometry discussed earlier (Schemes 1 and 2). In particular, it may denote that 2-NA can react with more of its naphthalene ring included in the CD cavity (Scheme 2).

The exception to the above pattern is the reaction of the two esters with α-CD. In this case, 1-NA is more reactive and we suggest that this ester can be perched on top of the narrow CD cavity in such a way that its ester group is reasonably accessible to the secondary hydroxy groups (**3**). By contrast, similar binding of 2-NA will direct the ester group more into the bulk medium (**4**), making attack by an anion of a secondary hydroxy group less easy. In fact, it may well mean that the naphthyl group of 2-NA has basically to come out of the α-CD cavity for reaction to take place (**4** ⟶ **4'**). Consistent with this suggestion, the reactivity of α-CD towards 2-NA is not different from that of TFE, as noted above, and it can be mediated by potential inhibitors (see below).



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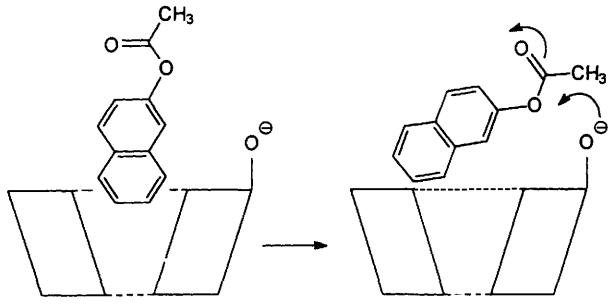

4 **4'**

Transition-state binding (K_{TS})

Here we make use of an approach for quantifying the stabilization of a transition state by a 'catalyst'.[22] As shown in detail elsewhere,[4,5] this approach is useful for reactions mediated by CDs and in particular for distinguishing between different modes of transition-state binding. Following Kurz,[22] we define an apparent constant (K_{TS}) for dissociation of the transition state of the CD-mediated reaction (TS·CD) into the transition state of the normal reaction (TS) and the CD [eqn. (8)]. This constant is a measure of the stabilization

$$K_{TS} = \frac{[TS][CD]}{[TS{\cdot}CD]} = \frac{k_u K_S}{k_c} = \frac{k_u}{k_2} \qquad (8)$$

of the transition state by the CD and variations of K_{TS} with structure can be used to probe transition-state binding.[4,5]

For the reactions of the two naphthyl acetates with the four CDs, values of K_{TS} vary from 0.09 to 8 mmol dm^{-3} (Table 1) which are not unusual values when compared with those for other aryl esters.[5] In large measure, the changes in K_{TS} parallel those in K_S so that the ratios $k_c/k_u = K_S/K_{TS}$ [from eqn. (8)] does not vary greatly: three ester/CD combinations have $k_c/k_u \sim 30$, a fourth has a ratio of 15, and for a fifth it is 9. Thus, as stated earlier, these acceleration ratios probably reflect a general similarity between initial-state and transition-state binding, at least for these five cases. The highest K_{TS}, corresponding to the weakest transition-state binding and the lowest k_c/k_u ratio of 3, belongs to 2-NA reacting with α-CD for which we have concluded that inclusion is not important in the transition state (see above and below). In agreement with this conclusion, K_{TS} for the reaction of 2-NA with TFE is very similar (Table 1).‡

For both esters, the strongest transition-state binding (lowest K_{TS}) is with β-CD, in agreement with the view that naphthalene rings fit well in its cavity.[1,3,13] Hydroxypropylation of the primary hydroxy groups of β-CD weakens this binding by factors of 2 and 3, whereas the same modification enhances substrate binding about twofold (Table 1). As a result, the accelerations observed with Hp-β-CD are four and six times less than with β-CD. If the stronger substrate binding by Hp-β-CD is due to its hydroxypropyl groups forming an intrusive floor to the CD cavity then its weaker transition-state binding may mean that the naphthyl groups of the esters are situated too high in the CD cavity to interact favourably with them in the transition state, consistent with the idea put forward earlier that the naphthyl groups may have to emerge from the β-CD cavity to some extent for the acyl transfer reaction to take place.

The effects of potential inhibitors

Previous work has shown that the cleavage of *p*-nitrophenyl acetate (and other alkanoates) by α-CD, β-CD, and by Hp-β-CD is not inhibited by many species that are expected to do

† In reaction with TFE, 2-NA is about twice as reactive as 1-NA (Table 1), as for reaction with *n*-alkylamines and mercaptoethanol, but 1-NA and 2-NA have very similar reactivities towards hydroxide ion: k_{OH} = 2.03 and 1.85 dm^3 mol^{-1} s^{-1}, respectively.

‡ We take the value of K_{TS} for TFE to be a measure of the bonding changes taking place in the transition state for cleavage and that the lower K_{TS} values found for most ester/CD combinations are indicative of the importance of CD inclusion.

so.[11] Furthermore, the kinetic effects of various potential inhibitors (PIs) were analysed successfully in terms of eqn. (7), consistent with mediation of the reaction by a molecule of PI [eqn. (5)]. These observations were taken as evidence that the ester comes out of the CD cavity during the acyl transfer reaction, in agreement with an earlier analysis of steric effects.[7d] In the present study, similar behaviour was found for the cleavage of 1-NA and 2-NA by CDs in two cases.

As discussed above, k_2 for the reaction of α-CD with 2-NA is the same as that for reaction of TFE (Table 1), implying that inclusion of the ester in the CD cavity is not significant in the transition state of the former reaction. In support of this assertion, the reaction of α-CD with 2-NA was not inhibited competitively by six linear alcohols and the results were analysed successfully using eqn. (7), consistent with the PI-mediated process in eqn. (5). Values of k_a for this process increase systematically with the strength of binding in the PI•CD complexes (Table 2) and there is a strong correlation of log k_a with pK_I ($= -\log K_I$): $r = 0.992$; slope $= 0.85 \pm 0.06$. This LFER, with a slope near 1, is good evidence that the PI is in the CD cavity during the PI-mediated reaction, so that the reaction might be better viewed as taking place between the PI•CD complex and the ester [eqn. (9)]. For this process,

$$\text{PI} + \text{CD} + \text{S} \underset{K_I}{\rightleftharpoons} \text{PI•CD} + \text{S} \xrightarrow{k_b} \text{products} + \text{PI} \quad (9)$$

values of k_b show very little variation with PI (Table 2)§ and they are only slightly less than k_2 for the reaction of 2-NA with α-CD alone, thereby providing additional evidence that 2-NA is not in the cavity of α-CD during the acyl transfer reaction.

Using the Kurz approach[5,22] for the third-order process involving a PI [eqn. (5) or eqn. (9)] we define the transition state parameters $K'_{TS} = [PI][CD•TS]/[PI•CD•TS] = k_2/k_3$ which is the same as k_c/k_a, since $k_2 = k_c/K_S$ and $k_3 = k_a/K_S$. This constant is a measure of the strength of binding of PI in the transition state of the PI-mediated reaction.[5,11] For 2-NA reacting with α-CD, values of K'_{TS} are only two to three times larger than K_I for the six alcohols acting as PIs (Table 2) and pK'_{TS} ($= -\log K'_{TS}$) correlates strongly with pK_I for the alcohols•α-CD complexes: $r = 0.992$; slope $= 0.85 \pm 0.06$ [Fig. 3(*a*)].¶ These observations also strongly support the view that the potential inhibitor PI is in the cavity of α-CD during the reaction with 2-NA, implying that the ester is not.

We have also obtained data for the effect of PIs on the cleavage of 1-NA by β-CD because we speculated that the ester must come out of the cavity to some extent during the reaction (see above, Scheme 1). Again, k_a increases substantially with the ability of the PI to bind to the CD and values of K'_{TS} are only slightly greater, than K_I (Table 2). For 12 alcohols of various types (1°, 2°, 3°, cyclic) there is a reasonable correlation ($r = 0.972$) of pK'_{TS} with pK_I, with a slope of 0.74 ± 0.06. The five linear alcohols give a much better correlation ($r = 0.990$) with a slope of 0.68 ± 0.06 [Fig. 3(*b*)], and the parameters for five alkanesulfonate ions ($r = 0.994$; slope $= 0.61 \pm 0.04$) are very similar [Fig. 3(*c*)].‖ In fact, the pK'_{TS} *vs.* pK_I data for these ROH and RSO_3^- essentially fall on the same straight line (Fig. 3). The slopes of 0.6–0.7 of these LFERs suggest that the mode of binding of the PIs in the transition state of the PI-mediated reaction is fairly similar to that in the PI•CD complexes.

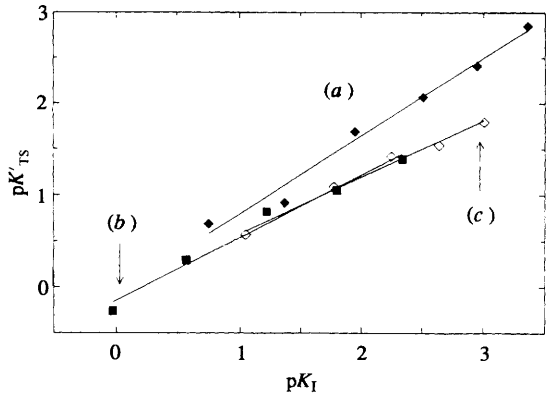

Fig. 3 Correlations of transition state binding (pK'_{TS}) of potential inhibitors with pK_I for their binding to the CD, for the cleavage of naphthyl acetates by CDs. The symbols are: (*a*) ◆, 2-NA + α-CD + linear alcohols; (*b*) ■, 1-NA + β-CD + linear alcohols; (*c*) ◇, 1-NA + β-CD + alkanesulfonate ions. The correlation lines are given in the text.

Taken altogether, the linear free energy relationships just presented constitute strong evidence that the naphthyl group of 1-NA comes out of the CD cavity to a considerable extent during the reaction with β-CD (Scheme 1), more so than in the case of 2-NA reacting with β-CD. For the latter reaction, experiments with a series of alcohols as potential inhibitors largely showed competitive inhibition, consistent with the naphthyl ring of 2-NA being included more deeply in the cavity of β-CD during the transition state of the cleavage reaction (Scheme 2).

Conclusions

The cleavage of 1- and 2-naphthyl acetates by cyclodextrins in basic solution shows a range of behaviour. There are subtle differences between the two isomeric esters which can be related to the modes of their binding to CDs. Also, there are more significant variations among the different CDs which are attributable to the sizes of their cavities.

Experimental

The two naphthyl acetates were purchased from Aldrich, as was α-CD. The other cyclodextrins were obtained from Wacker-Chemie (Munich, Germany) and the γ-CD was purified by recrystallization.[12b]

Cleavage reactions were carried out by 1:1 mixing in a stopped-flow apparatus. One syringe contained the phosphate buffer (0.4 mol dm^{-3}, pH 11.6) and the other contained ester and CD at twice the concentrations desired in the reaction. Substrate solutions were made by dilution of 0.1 mol dm^{-3} stock solutions in spectral grade acetonitrile. After mixing in the stopped-flow apparatus the ester concentrations in the reaction medium were 50 or 100 μmol dm^{-3}.

The kinetics of ester cleavage were followed by monitoring the first-order production of the product naphtholate ion at 244 nm or 333–350 nm, using an Applied Photophysics SX17MV stopped-flow spectrophotometer, with the observation cell kept at 25.0 ± 0.1 °C. Absorbance traces consisting of 400 points covering five to seven half-lives were collected and first-order rate constants were estimated from non-linear least-squares fitting of a first-order exponential to these data. The recorded rate constants (k_{obs}) were taken as the averages of 5 to 10 determinations. Sometimes, with the slowest reactions, the absorbance traces at 244 nm were distorted due to a downward

§ For the process depicted in eqn. (5) the third-order rate constant $k_3 = k_a/K_S$ while for that shown in eqn. (9) $k_3 = k_b/K_I$. Thus, $k_b = k_a K_I/K_S$.[11]

¶ For the cleavage of *p*-nitrophenyl acetate by α-CD in the presence of 13 different alcohols, the corresponding slope is 1.03 ± 0.04.[11b]

‖ These slopes for ROH and RSO_3^- are close to those (0.67 and 0.75) for the cleavage of *p*-nitrophenyl acetate by β-CD in the presence of the same PIs.[11b]

drift of the 'infinity' readings which seemed to be due to photogradation. This drift was corrected for during the data analysis, using software supplied with the spectrophotometer. The problem can be minimized by working at longer wavelength (330–350 nm) but the absorbance change is smaller there and so the traces are noisier.

Rate constants for the hydrolysis of 1-NA and 2-NA in basic solution were in good agreement with literature values.[23,24] The constants k_c and K_S in Table 1 were obtained by non-linear fitting[25] of eqn. (3) to k_{obs} values obtained at [CD] = 0–10 mmol dm^{-3} (α-CD, β-CD), or 0–20 mmol dm^{-3} (Hp-β-CD, γ-CD) (*e.g.*, Fig. 1). In no case did we observe significant deviations from eqn. (3) at high [CD] that could be attributed to the onset of 2:1 (CD:ester) binding, such as found in other studies.[10,12]

The experiments with potential inhibitors were carried out in the manner detailed earlier for nitrophenyl esters,[11] with $[CD]_0$ fixed at 10 mmol dm^{-3}. Six rate constants (k_{obs}) were obtained for a range of $[PI]_0$ governed largely by the solubility of PI. Typical maximum concentrations (in mmol dm^{-3}) used were: EtOH, 500; Pr^{n}OH, 400; Bu^{n}OH, 200; Pen^{n}OH, 100; Hex^{n}OH, 10; Hept^{n}OH, 3.5. Some other examples can be seen in Fig. 2. Estimations of k_a values were carried out by analysis of the variations of k_{obs} with [PI] in terms of eqn. (7), using the appropriate K_S from Table 1 and K_I values from the literature.[20,21] Calculations were executed in a spreadsheet, as previously.[11]

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