Catalysis of the enolization of indan-2-one by cyclodextrins in aqueous solution

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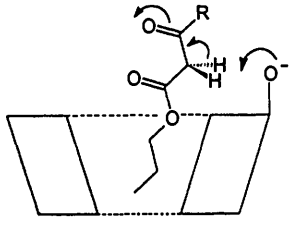
In basic aqueous solution, enolate formation from indan-2-one (2, pK_a = 12.2) exhibits saturation kinetics when cyclodextrins (CDs) are added, consistent with the formation of 1:1 complexes between 2 and the CDs. With α-CD, β-CD, γ-CD, 'hydroxyethyl-β-CD' and 'hydroxypropyl-β-CD', the reaction is accelerated up to 22-fold, but 'dimethyl-β-CD' slows it down by *ca.* 46%. All of the CDs (pK_a = 12.2) are more reactive towards 2 than is trifluoroethanol (pK_a = 12.4). Kinetic parameters for the CD-catalysed deprotonation are discussed in terms of the differences between transition-state binding and initial-state binding, and of the structures of the various CDs. It is concluded that anions of the CDs act as general bases towards 2, facilitated by partial inclusion of the transition state in the CD cavity, the extent of which depends on the CD. Enolate formation catalysed by β-CD is slowed by simple alcohols (propan-1-ol to heptan-1-ol), but it is not really inhibited by them, even though they bind to β-CD. Apparently, deprotonation of 2 by an anion of β-CD can still take place with an alcohol in the CD cavity, albeit more slowly.

Cyclodextrins (CDs) form host–guest complexes with many species in aqueous solution.[1,2] Within such complexes, chemical reactions of the included guests may take place, and the effects of inclusion on the reactivity vary widely according to the guest, the CD and the reaction. In some cases, the rate of reaction is greatly reduced, leading to the use of CDs as stabilizers,[1b,2a] but of more interest to us, CDs can also accelerate reactions.[1,3,4] In most instances, the CD host simply provides a confined environment for the reaction that is less polar than the bulk solvent. However, in other cases the CD participates directly in the reaction and undergoes covalent change, itself.[1,3,4] For example, in basic solution an ionized secondary hydroxy group of a CD host may act as a nucleophile towards a guest ester, resulting in acyl transfer to the CD.[1,3-5] Similarly, an ionized secondary hydroxy group may function as a base toward included substrates, as in the general base-catalysed attack of water on activated esters[6] and in the CD-catalysed enolization of oxazolones[7] and of β-keto esters in basic solution.[8,9]

For the deprotonation of simple β-keto esters of the structure $RCOCH_2COOR'$ by α-CD[1] and β-CD[1] it was found that the parameters for substrate binding and catalysis are quite sensitive to the size of the alkoxy group –OR', but not particularly to that of the acyl group RCO. Accordingly, it was concluded that both substrate binding and catalysis of enolate formation by the CDs involve inclusion of the alkoxy group of the keto ester (**1**), rather than inclusion of its acyl group.[4,9]



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The present paper reports a study of the catalysis of enolization of indan-2-one (**2**) by several cyclodextrins in aqueous base. For a simple ketone, **2** has a relatively low pK_a of 12.2, and its enolate can be observed easily in aqueous solution at high pH.[10] Moreover, the pK_a of **2** is virtually the same as those of α-CD and β-CD (12.2, 12.3),[11] so that deprotonation of indan-2-one by a cyclodextrin anion should be more or less thermodynamically neutral ($\Delta G^\circ \approx 0$) and relatively fast. Proton abstraction from **2** by a CD anion might be facilitated if **2** can bind to the CD in an orientation that is favourable for the proton transfer. So, from the outset, there were three main objectives of the present study: (*i*) to establish if the enolization of indan-2-one can be catalysed by various CDs; (*ii*) to quantify any catalytic effects that were found; (*iii*) to try to assess the importance of inclusion to the CD-catalysed deprotonation. These objectives have been reached.

Results

Using stopped-flow spectrophotometry, we have measured the kinetics of equilibration of indan-2-one (**2**) and its enolate in basic aqueous solution. First, to check our approach, we looked at the behaviour of **2** in NaOH solutions (0.001–0.10 mol dm^{-3}, I = 0.10 mol dm^{-3}), under conditions where the observed rate constant (k_{obs}) has forward and backward components, due to enolate formation by hydroxide ion and reprotonation (by water) [eqn. (1)].[10] From the linear dependence of

$$k_{obs} = k_1[OH^-] + k_{-1} \quad (1)$$

k_{obs} on $[OH^-]$ we obtained $k_1 = 214 \pm 7$ dm^3 mol^{-1} s^{-1} and $k_{-1} = 5.53 \pm 0.61$ s^{-1}, in good agreement with previous values. Together, these values yield $K_a = k_1K_w/k_{-1} = (6.20 \pm 0.48) \times 10^{-13}$ mol dm^{-3} and pK_a = 12.21 ± 0.03, whereas analysis[10c] of the $[OH^-]$ dependence of the absorbance changes that accompany the reaction gave pK_a = 12.23 ± 0.02.† These kinetic results and both of the pK_a values are in excellent agreement with those obtained by Pollack and Kresge and their respective co-workers in two earlier studies.[10]

For reactions in the presence of cyclodextrins the reaction

† For consistency with previous workers,[10] we have used $K_w = 1.59 \times 10^{-14}$ mol^2 dm^{-6} (pK_w = 13.80) for an ionic strength of 0.10 mol dm^{-3}.

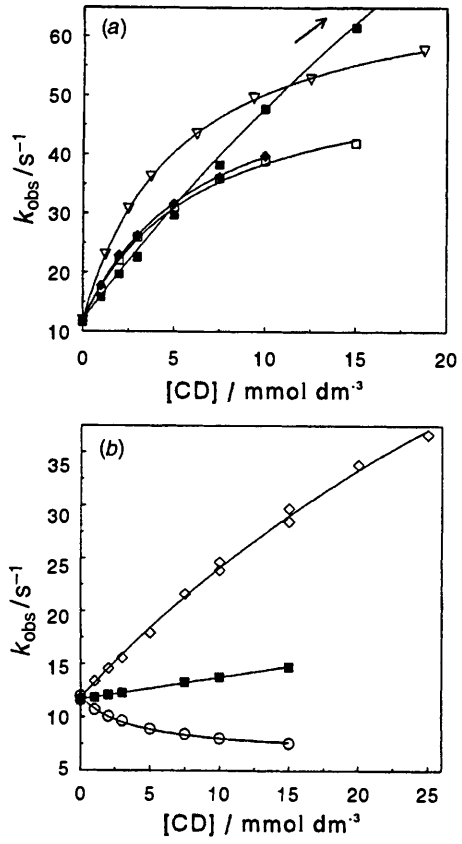


Fig. 1 Rate constants for enolate formation from indan-2-one in the presence of cyclodextrins and trifluoroethanol, at pH 11.6. Except for TFE, the curves are calculated for saturation kinetics from eqn. (3), using fitted constants given in Table 1. The symbols are: (*a*) α-CD, ■; hp-β-CD, ▽; β-CD, ◆; he-β-CD, □; (*b*) γ-CD, ◇; TFE, ■; diMe-β-CD, ○. The actual data for α-CD (12 points) extend out to 100 mmol dm^{-3}. Note that the data points for he-β-CD and β-CD are virtually coincident so that the parameters for these two CDs are essentially identical (Table 1).

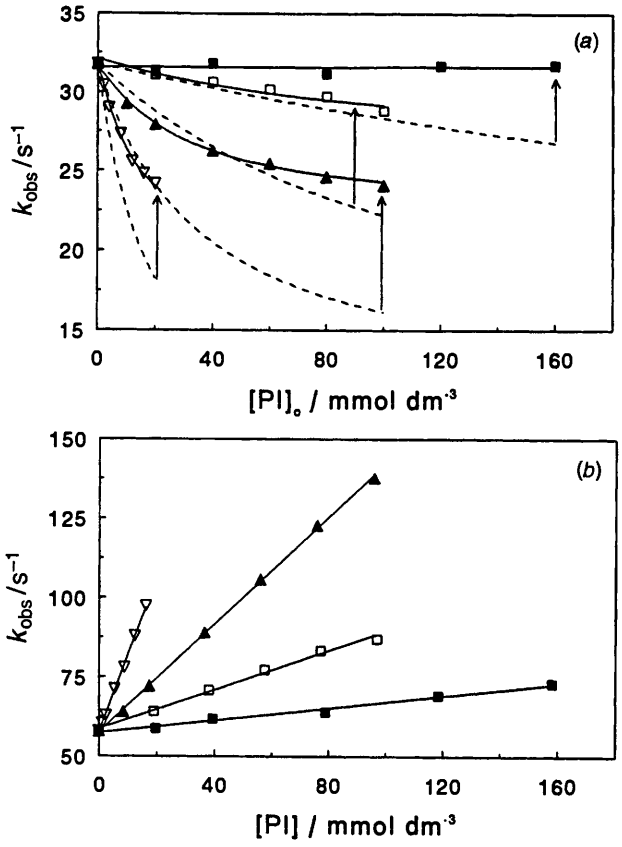


Fig. 2 Examples of the effects of added alcohols on the deprotonation of indan-2-one by β-CD (5.00 mmol dm^{-3}). The symbols are: PrOH, ■; BuOH, □; $C_5H_{11}OH$, ▲; $C_6H_{13}OH$, ▽. The data for heptan-1-ol are not shown because they would not readily be discernible on the scale that is convenient for the other alcohols. Part (*a*) shows the dependence of k_{obs} on the total alcohol concentration, where the dashed curves are those calculated for competitive inhibition and the solid curves are those calculated for alcohol-mediated reaction [eqn. (6)]. Part (*b*) shows the linear dependence of k_{corr} on the concentration of free alcohol [eqn. (7)], for the same data as in part (*a*); the slopes of such plots afford the rate constants k_a given in Table 2.

medium was a 0.2 mol dm^{-3} phosphate buffer of pH 11.6.‡ Reactions were carried out in the presence of the three principal CDs, α-CD, β-CD, γ-CD,[1] and of three chemically-modified derivatives of β-CD, 'dimethyl-β-cyclodextrin' (diMe-β-CD), 'hydroxyethyl-β-cyclodextrin' (he-β-CD) and 'hydroxypropyl-β-cyclodextrin' (hp-β-CD).[1,2a,12] Pseudo-first-order rate constants (k_{obs}) were obtained over a range of CD concentrations and in all cases the CDs gave rise to simple saturation kinetics[1,3,4,5a] (Fig. 1). The behaviour observed conforms very well to reaction of the substrate (S) in the medium [eqn. (2*a*)], along

$$S \xrightarrow{k_u} \text{products} \qquad (2a)$$

with reaction through a substrate–CD complex [eqn. (2*b*)], or

$$S + CD \rightleftharpoons S\text{–}CD \xrightarrow{k_c} \text{products} \qquad (2b)$$

‡ It should be noted that the pH of the experiments (11.6) is less than the pK_a of indan-2-one (12.2), so that only about 20% of the ketone is converted to its enolate in the reaction. Experiments were carried out in this way so that the CDs were largely unionized and the K_s values obtained from the saturation kinetics basically refer to the binding of **2** to neutral CDs. The pH used also means that the reaction followed was not just enolate formation but equilibration of **2** with its enolate, so that k_{obs} has forward and reverse components,[10] as remarked already. However, the forward and backward processes have the same transition state and so will experience the same transition state stabilization by catalysts. In what follows we will discuss the catalysis in terms of 'enolate formation', while bearing in mind that it is really an equilibration that was studied.

its kinetic equivalent.[4] For these two processes, taking place in competition, the variation of k_{obs} with [CD] may be represented by eqn. (3).

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

Most of the data obtained are shown in Fig. 1, together with saturation curves calculated from eqn. (3) and the fitted constants, k_c and K_S, given in Table 1. With the sole exception of diMe-β-CD, values of k_{obs} increase with added [CD] because $k_c > k_u$, meaning that the deprotonation reaction is catalysed in most cases. In the unique case of diMe-β-CD [Fig. 1(*b*)], k_{obs} decreases with added [CD] because $k_c < k_u$, but enolate formation is not completely inhibited since k_c is far from negligible (Table 1).

The pK_a of trifluoroethanol (TFE) is 12.4,[13] close to that of the CDs (12.2–12.13),[11] and for comparative purposes catalysis of the deprotonation of **2** by TFE, reacting as its anion, was also studied in the same basic phosphate buffer. We found only a linear increase in k_{obs} with TFE concentration [Fig. 1(*b*)], and the appropriate second-order rate constant (k_2, Table 1) was obtained from the slope.

For reasons which will become more apparent in the Discussion, we have also looked at the effects of some simple alcohols on the deprotonation of indan-2-one catalysed by β-CD. Since alcohols bind to β-CD,[5f] they might be expected to inhibit the

Table 1 Constants for the deprotonation of indan-2-one in the presence of cyclodextrins and trifluoroethanol[a]

CD	k_u/s^{-1}	k_c/s^{-1}	k_c/k_u	K_S/mmol dm^{-3}	k_2/dm^3 mol^{-1} s^{-1}	K_{TS}/mmol dm^{-3}	EM/mol dm^{-3}
α-CD	11.9	262 ± 5	22	59.5 ± 2.1	4 400	2.7	1.3
β-CD	11.7	57.9 ± 0.9	5.0	6.49 ± 0.24	8 900	1.3	0.28
he-β-CD	11.6	55.8 ± 0.5	4.8	6.42 ± 0.17	8 700	1.3	0.27
hp-β-CD	11.7	70.4 ± 0.3	6.0	5.23 ± 0.07	13 500	0.87	0.34
diMe-β-CD	12.0	6.53 ± 0.12	0.54	3.81 ± 0.22	1 700	7.0	0.03
γ-CD	11.8	98.2 ± 9.6	8.3	60.5 ± 8.6	1 600	7.0	0.48
TFE	11.6	—	—	—	206 ± 3[b]	56	—

[a] At 25 °C, in an aqueous phosphate buffer at pH 11.6. The constants K_S and k_c were obtained by fitting of eqn. (3) to kinetic data; their uncertainties are the standard errors from the fitting. They were used to construct the curves plotted in Fig. 1. The derived constants are: $k_2 = k_c/K_S$ and $K_{TS} = k_u/k_2$. Effective molarities (EM) are estimated from k_c/k_2(TFE). [b] Trifluoroethanol does not give saturation kinetics and k_2 is simply the slope of the linear dependence of k_{obs} *vs.* [TFE].

catalysis by lowering the available β-CD concentration, causing a reduction in k_{obs} in accordance with eqn. (3). This type of behaviour, which is known as 'competitive inhibition',[14] is observed for the cleavage of some esters by cyclodextrins, but in other cases the observed rate retardation is much less than expected.[5f,15] In a similar manner, we have found that five linear alcohols (propan-1-ol to heptan-1-ol) do not slow down the catalysis of deprotonation of **2** by β-CD to the extent appropriate for competitive inhibition, as shown with the examples of Fig. 2(*a*). The discrepancy can be accounted for with a process in which CD catalysis can take place with one molecule of an alcohol bound to the β-CD in the transition state.

The kinetic data for enolization in the presence of alcohols were analysed to obtain rate constants for an alcohol-mediated process, using the approach developed in earlier work on the effects of potential inhibitors on ester cleavage by cyclodextrins.[15a] In this approach allowance is made for binding of the potential inhibitor (PI) to the cyclodextrin [eqn. (4)] and

$$PI + CD \overset{up}{\underset{K_I}{\rightleftharpoons}} PI\text{–}CD \qquad (4)$$

for a PI-mediated process [eqn. (5)] which operates so as to

$$PI + CD + S \overset{up}{\underset{K_S}{\rightleftharpoons}} PI + CD\text{–}S \xrightarrow{k_a} products + PI \qquad (5)$$

compensate for the effects of competitive inhibition. The involvement of the latter process means that eqn. (3) must be expanded to eqn. (6), but for easier analysis we rearrange it

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

to eqn. (7). The latter equation, which separates the background

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

reaction [eqn. (2*a*)] from the two processes involving the CD, requires a linear dependence of k_{corr} on [PI], whose slope is the rate constant for the PI-mediated process, k_a.

Examples of the linear dependence prescribed by eqn. (7) are given in Fig. 2(*b*), corresponding to the observed data presented in Fig. 2(*a*). The values of k_a obtained for the five alcohols are collected in Table 2, along with some derived constants.

Discussion

Before considering the results in detail, we will summarise the differences between the cyclodextrins used. The three principal CDs, α-CD, β-CD and γ-CD, are comprised of six, seven and eight glucose units, respectively.[1] The cavities of all three hosts have the same depth (*ca.* 7 Å), but their widths increase from α-CD (*ca.* 5.0 Å) to β-CD (*ca.* 7.0 Å) to γ-CD (*ca.* 9.0 Å), which affects their abilities to include guests of different sizes.[1,2] In 'hydroxyethyl-β-cyclodextrin' (he-β-CD) and 'hydroxypropyl-β-cyclodextrin' (hp-β-CD) about six of the seven primary hydroxy groups of β-CD are alkylated[1,2a,12] which has the effect of narrowing the opening of the primary side of the CD cavity and possibly of forming an intrusive floor[16] to it. In 'dimethyl-β-cyclodextrin' (diMe-β-CD), all of the primary OHs are methylated, as well as the secondary OHs at C-2 of each glucose,[12] resulting in a cavity that is somewhat extended and more hydrophobic than that of β-CD. The structural differences between the CDs will affect their binding of initial states and transition states, though not necessarily in the same way because the geometry that gives the strongest binding of the substrate may be quite different from that which is optimal for reaction.

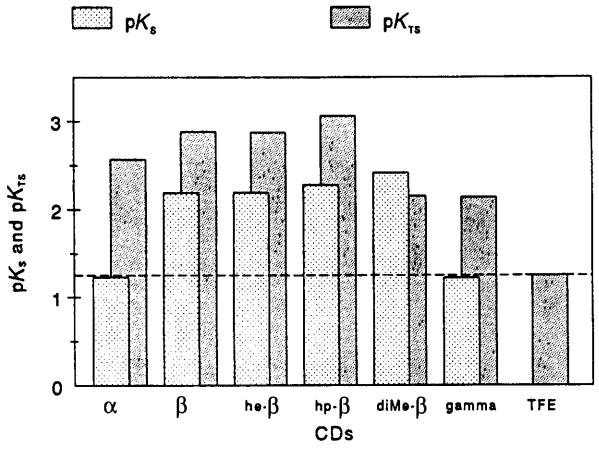


Fig. 3 Comparison of the substrate binding (pK_S) and transition-state binding (pK_{TS}) of indan-2-one for different cyclodextrins. The value of pK_{TS} for trifluoroethanol (TFE) is taken to represent the component of transition-state binding that is due solely to the covalency changes associated with proton transfer.

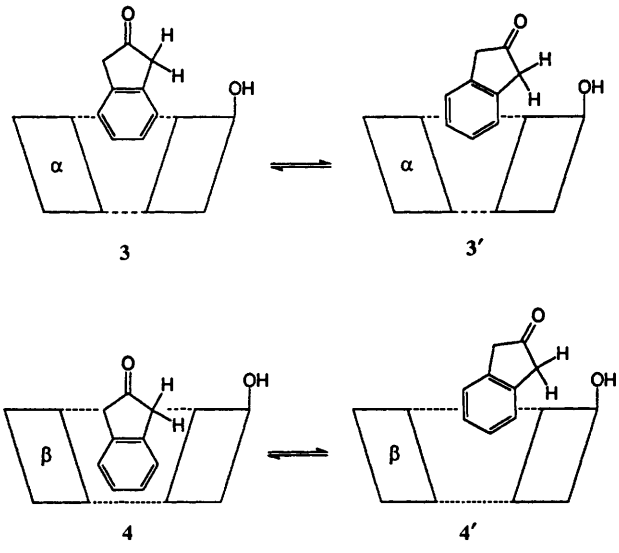
Substrate binding (K_S)

The strength of binding of indan-2-one (**2**) to the six CDs is depicted in Fig. 3, plotted as values of pK_S = −log K_S. These values follow the order: diMe-β-CD > hp-β-CD ≈ β-CD = he-β-CD > α-CD ≈ γ-CD, which is reminiscent of the order followed by simple naphthalene derivatives which bind better to β-CD than to α-CD or γ-CD.[1b,5f,17] So, it seems that **2**, which is similar in size to naphthalene, is too big to fit well into the small cavity of α-CD and too small to fill adequately into the large cavity of γ-CD. Consistent with these ideas, space-filling [Corey–Pauling–Koltum (CPK)] models suggest that **2** can only partially enter the cavity of α-CD, either as in structure **3** or in structure **3'**. Of the two, **3'** appears to be better suited for enolate formation since it brings two of the enolizable hydrogens of **2** close to secondary hydroxy groups at the rim of the cavity. By contrast, **2** can sit more deeply in the cavity of β-CD (**4**) and for it to attain a geometry suitable for proton transfer to an ionized OH it must sit higher in the cavity and to one side (**4'**). With γ-CD the fit is not snug and **2** may sit deep in the cavity, in a position that is not favourable for reaction.

Table 2 Constants for the effects of alcohols on the deprotonation of indan-2-one in the presence of β-cylodextrin[a]

ROH	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}
PrOH	269	96.7 ± 5.4	4010	599
BuOH	60.3	307 ± 13	2850	189
$C_5H_{11}OH$	15.9	860 ± 10	2101	67.3
$C_6H_{13}OH$	4.57	2410 ± 55	1700	24.0
$C_7H_{15}OH$	1.41	5520 ± 210	1200	10.5

[a] At 25 °C, in an aqueous phosphate buffer of pH 11.6. Values of K_I are taken from the literature (see ref. 5*f*). Values of k_a are the slopes of linear plots of k_{corr} *vs.* [ROH] [*e.g.* Fig. 2(*b*)], based on eqn. (7); k_b values are calculated from k_aK_I/K_S and $K'_{TS} = k_c/k_a$.



The differences between the binding of **2** to the four derivatives of β-CD are quite small. Between β-CD and he-β-CD there is no difference, but with hp-β-CD the binding is slightly stronger which may result from an intrusive floor[16] provided by the 2-hydroxypropyl groups on the primary side of the CD cavity. The strongest substrate binding is found with diMe-β-CD which may result from additional hydrophobic interactions or van der Waals contacts with the methyl groups on the secondary side of the cavity.

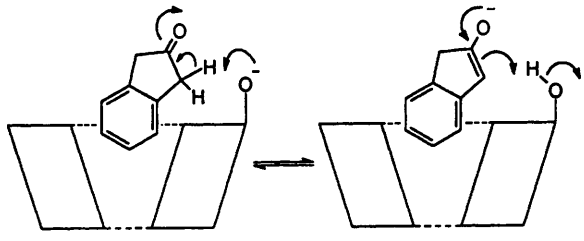
Substrate binding is important in as much as it gives rise to saturation kinetics, and if the substrate can fit the cavity then the transition state may do so also, but the strength of substrate binding conveys no information about the catalytic process. To find out about this, one has to look at kinetic parameters.[4]

Rate acceleration (k_c/k_u)

The maximal acceleration that is attainable at saturating levels of the CD is given by the ratio k_c/k_u. For enolate formation from indan-2-one catalysed by CDs, this ratio ranges from 0.54 to 22 (Table 1) as the reaction is slowed by diMe-β-CD, but it is accelerated by the others (Fig. 1). Note that there is no clear correlation between the acceleration and the strength of substrate binding to the CD. If anything, the inverse holds: the largest acceleration is seen with α-CD, which binds weakly, and the lowest is that for diMe-β-CD, which binds **2** about 16 times more strongly. As will be more apparent later, the largest acceleration is observed with α-CD because it has the largest difference between the initial-state binding and transition-state binding, and the retardation by diMe-β-CD arises because it binds the substrate more strongly than the transition state.

Catalytic ability (k_2)

Even though the observed saturation kinetics (Fig. 1) indicate that indan-2-one forms 1 : 1 complexes with the various CDs, it does not necessarily follow that these (or any) complexes are involved in the catalysis.[4] It could transpire that the CD anions simply function as general base catalysts, without significant inclusion of the substrate in the CD cavity in the transition state. If such was the case, the catalytic coefficients of the various CDs (k_2, Table 1) should all be much the same and hardly different from that of TFE, which has a similar pK_a value (*vide supra*). In contrast, we found that the CDs exhibit a range of catalytic ability and all of them are better catalysts than TFE. Their reactivities follow the order: hp-β-CD > β-CD ≈ he-β-CD > α-CD > diMe-β-CD ≈ γ-CD > TFE, and at the extreme hp-β-CD reacts 65 times faster than TFE. Even the two weakest CD catalysts, diMe-β-CD and γ-CD, are eight times more effective than TFE. Thus, it seems that inclusion of indan-2-one in the CD cavities (Scheme 1) does make some contribution to



Scheme 1

transition-state stabilization,[4] albeit modest, ranging from 5 to 10 kJ mol^{-1} (for γ-CD to hp-β-CD). Note that diMe-β-CD and γ-CD have very similar reactivities towards **2**, even though one retards the reaction and the other accelerates it. The difference between the two arises because diMe-β-CD binds **2** appreciably more strongly than does γ-CD, whereas their strengths of transition-state binding are the same (*vide infra*).

Comparison with the reactivity of TFE towards indan-2-one also provides a way of estimating the effective molarities (EMs) of the proton transfer reactions taking place within the substrate–CD complexes. Values of EM are a measure of the efficiency of an intramolecular reaction compared with a suitable intermolecular model.[18] In the present case, approximate EM values for the CD-catalysed reactions can be estimated by dividing k_c for reaction within the supermolecule[19] substrate–CD by k_2 for the TFE reaction, and they vary between 0.03 and 1.3 mol dm^{-3} (diMe-β-CD and α-CD), with most of them ranging between 0.27 and 0.48 mol dm^{-3} (Table 1). These values are low, particularly when compared with the extraordinarily high values that are sometimes found for intramolecular nucleophilic attack, but they are not so unusual for intramolecular general base (or general acid) catalysis,[18a] nor are they unusual for reactions involving CDs which only show high EM values (up to 10^4 mol dm^{-3}) in the case of very fast acyl transfers.[18b] Conceivably, a much higher EM for proton transfer could be found with a substrate which binds to a CD in a geometry that forces the acidic proton of the substrate up against the basic site of the catalyst, and in an orientation that is conducive to proton transfer (*cf.* Scheme 1).

Transition-state binding (K_{TS})

To probe the transition-state binding of indan-2-one by the CD catalysts we use an approach devised by Kurz.[20a] As demon-

strated previously,[4] this approach is applicable to reactions involving cyclodextrins and it has been especially helpful in distinguishing between different modes of transition-state binding.[4,5h-l,9,15,21] For the present purposes, we define an apparent constant (K_{TS}) for dissociation of the transition state of the CD-catalysed reaction (TS–CD) into the transition state of the normal reaction (TS) and the CD catalyst [eqn. (8)].

$$K_{TS} = \frac{[TS][CD]}{[TS\text{–}CD]} = \frac{k_u K_S}{k_c} = \frac{k_u}{k_2} \quad (8)$$

This quasi-equilibrium constant K_{TS}, or better $pK_{TS} = -\log K_{TS}$, is a measure of the strength of stabilization of the transition state by the CD catalyst,[4,18b] and Fig. 3 shows the variation of pK_{TS} with the CD, in comparison to that of pK_S for substrate binding. While there is some parallelism between the two parameters, it is far from strong. As discussed already, the substrate binding follows the order: diMe-β-CD > hp-β-CD ≈ β-CD = he-β-CD > α-CD > γ-CD ≫ TFE, where the last is non-binding. In contrast, for transition-state binding the order is: hp-β-CD > β-CD = he-β-CD > α-CD > diMe-β-CD ≈ γ-CD > TFE, the same as for k_2. The difference between the two orders is mainly in the placement of diMe-β-CD, and so it is associated with the effects of alkylation on the secondary side, as opposed to the primary side, which is also present in both he-β-CD and hp-β-CD. Whereas dimethylation of β-CD strengthens substrate binding (by about 70%) it weakens transition-state binding (by 530%).§ The latter may result from three effects arising from methylation of half of the secondary OHs: steric hindrance to proton transfer, reduction of the number of reactive sites and the raising of the effective pK_a of the CD. If all of the secondary OHs of β-CD are equally reactive, or those at C-2 are more reactive, then removal of the OHs at C-2 would reduce reactivity by a factor of two, or more. In the case of ester cleavage, which is expected to be more sensitive to steric effects, the decrease in reactivity caused by dimethylation is greater (factors of 10–15).[5k] Perhaps then the less efficient enolate formation by diMe-β-CD is mainly due to removal of the most reactive hydroxy groups or to it being less acidic.

According to eqn. (8), the limiting acceleration arises from the differences between the strength of transition-state binding and substrate binding: $k_c/k_u = K_S/K_{TS}$. This means that the difference between pK_{TS} and pK_S for each CD in Fig. 3 reflects the corresponding value of $\log(k_c/k_u)$. Thus, as pointed out already, the largest acceleration is seen with α-CD because it binds the transition state for deprotonation appreciably more strongly than the substrate, and the retardation by diMe-β-CD arises because it binds the substrate more strongly than the transition state. The strongest transition-state binding is observed with hp-β-CD, but it does not show a large acceleration because it also binds the substrate comparatively well.

The bar graphs of pK_{TS} in Fig. 3 may be used to emphasize another aspect. The lowest value of pK_{TS} is that for TFE, which is related solely to the covalency changes associated with reaching the transition state for proton transfer, devoid of any influence of inclusion. Compared with this, the higher values of pK_{TS} for the CDs reflect the significant contribution of inclusion to the CD-catalysed reactions (Scheme 1). Of course, this is effectively the same argument as made in terms of k_2, above.

Effects of alcohols

Several studies of ester cleavage by CDs have shown that the reaction is not always inhibited by species that might be expected to do so.[5l,15] Moreover, the effects of the potential inhibitors (PIs) were successfully treated by eqn. (7), consistent with mediation of the reaction by a single molecule of PI [eqn. (5)]. As a result, it was concluded that the esters emerge from the CD cavity to some extent during the cleavage reaction, in agreement with analysis of steric effects.[5f] In like manner, the present study shows that catalysis of enolate formation from indan-2-one by β-CD is not totally inhibited by simple linear alcohols [Fig. 2(*a*)] and analysis of the data in terms of eqn. (7) [Fig. 2(*b*)] has provided rate constants (k_a) for mediation of the reaction by the alcohols [eqn. (5)].

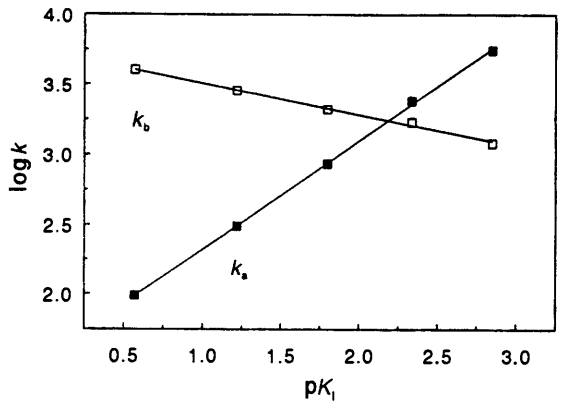


Fig. 4 Rate constants for the enolization of indan-2-one calalysed by β-CD and mediated by simple alcohols (Table 2). Correlations of $\log k_a$ [eqn. (5)] and $\log k_b$ [eqn. (9)] with pK_I for the binding of the alcohols to β-CD. Note that because $K'_{TS} = k_2/k_3 = k_c/k_a$ and k_c is a constant for **2** and β-CD, the correlation of pK'_{TS} with pK_I is the same as that for $\log k_a$, except for the intercept term.

Values of k_a (Table 2) increase strongly and regularly with the ability of the alcohol to bind to β-CD and a plot of $\log k_a$ *versus* pK_I is linear ($r = 0.9998$) with a slope of 0.776 ± 0.009 (Fig. 4), consistent with significant inclusion of the alcohol in the CD during the alcohol-mediated reaction.¶ Perhaps, then, this process should be viewed as arising from the reaction of indan-2-one with β-CD that has a molecule of the alcohol bound in its cavity [eqn. (9)]. Rate constants (k_b) for this process are also given in Table 2.‖

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

Values of k_b decrease with increasing alcohol size and the linear plot of $\log k_b$ against pK_I has a slope of −0.224 ± 0.009 (Fig. 4). Thus, as the alcohol occupying the CD cavity becomes larger, the process in eqn. (9) is made progressively more difficult, with k_b decreasing from 4000 to 1200 $dm^3\ mol^{-1}\ s^{-1}$, compared with $k_2 = 8900\ dm^3\ mol^{-1}\ s^{-1}$ for the reaction of **2** with β-CD, alone.††

For the third-order process involving a PI [eqns. (5) or (9)], we define the transition-state parameter $K'_{TS} = [PI][CD\text{–}TS]/[PI\text{–}CD\text{–}TS] = k_2/k_3$, using the Kurz approach,‡‡[4,15] to provide a measure of the strength of binding of PI in the transition state of the PI-mediated reaction. In the present case, where

§ The effects of dimethylation on initial-state and transition-state binding for ester cleavage by β-CD are in the same directions, but larger.[5k]

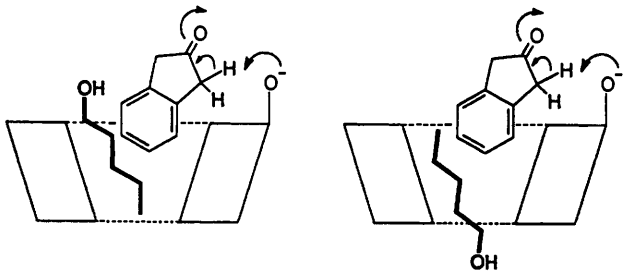
¶ It should not be inferred that the effects of the alcohols arise from their anions, which are present at very low concentrations ($<10^{-5}$ mol dm^{-3}), acting as general bases, in the manner of the TFE anion. For such to be the case, the alkoxide ions would have to have very high catalytic coefficients (10^6–$10^8\ dm^3\ mol^{-1}\ s^{-1}$), much greater than those for hydroxide ion or the TFE anion (*ca.* $200\ dm^3\ mol^{-1}\ s^{-1}$). Also, the effects of the five alkoxide ions should be all much the same and they should not show the strong dependence of k_a on the structure of the alcohol and its ability to bind to β-CD (*vide supra*, Fig. 4).

‖ Note that if the PI-mediated reaction proceeds as given in eqn. (5) the overall third-order rate constant is $k_3 = k_a/K_S$. Alternatively, for the reaction according to eqn. (9), $k_3 = k_b/K_I$, and so $k_b = k_a K_I/K_S$.[15]

†† Note that if $k_b = k_2$ then addition of the PI would have no effect on k_{obs} since PI–CD and CD would have exactly the same reactivity towards the substrate.

‡‡ Note that $K'_{TS} = k_2/k_3$ is the same as k_c/k_a, since $k_2 = k_c/K_s$ [eqn. (2*b*)] and $k_3 = k_a/K_S = k_b/K_I$ (see footnote ‖, above).

alcohols are the PIs binding to β-CD, the variation of pK'_{TS} for the transition state with pK_I for the initial state is linear ($r = 0.9998$)
with a slope of 0.776 ± 0.009, as for $\log k_a$. This LFER also supports the view that an alcohol molecule can be in the cavity of β-CD during deprotonation of indan-2-one. The slope approaching one could be taken to mean that the binding of the alcohols in the transition-state structure composed of **2**–β-CD–alcohol is quite similar to that in the binary β-CD–alcohol complexes, possibly as in structure **5**. Alternatively, the orientation of the alcohol may be inverted, as in **5'**, if binding in this manner also has a linear dependence of pK_I on chain length, as is the case for the normal mode.[5f]



5 **5'**

Regardless of the finer details, it is clear that having a single molecule of a simple alcohol in the cavity of β-CD reduces its reactivity but it does not eliminate it. So, while inclusion of indan-2-one in the CD cavity makes a definite contribution to stabilization of the transition state for proton abstraction, the substrate may partially emerge from the cavity during the reaction. Presumably, a substrate whose deprotonation was very strongly accelerated, and which enjoyed greater transition-state stabilization due to inclusion in the CD cavity, would be more sensitive to potential inhibitors such as alcohols and more likely to display true competitive inhibition.

Conclusions

With the exception of 'dimethyl-β-cyclodextrin', cyclodextrins accelerate enolate formation from indan-2-one **2** in basic solution. Saturation kinetics indicate the formation of 1:1 complexes between **2** and all six of the CDs studied. The CDs, reacting as their anions, are more reactive towards **2** than is trifluoroethanol, reacting as its anion, indicating that inclusion of **2** in the CD at the transition state (Scheme 1) is important to some extent. The kinetic effects of the CDs can be rationalized in terms of their cavity sizes and the requirements of transition-state binding relative to initial-state binding. For β-CD, the effects of added alcohols are consistent with partial emergence of **2** the substrate from the cavity during the proton-transfer process. More efficient catalysis might be found with a substrate that has more similar initial-state and transition-state binding, *i.e.* with a substrate that binds to a CD in a geometry that is much more appropriate for facile proton transfer.

It should be recognized that the present study was carried out to provide an overview of the effects of CDs on the enolization of indan-2-one. A proper dissection of the effects of CDs on the rate constants k_1 and k_{-1}, and hence on the pK_a of **2**, will require a much more detailed study, with experiments at various pH values using different methodologies to study the forward and backward processes separately. In particular, one could use enolate trapping, *e.g.* with a halogen scavenger, to isolate the effects on k_1, and for the reverse reaction, one could use enolate quenching in buffers at pH $\ll pK_a$ to find out the effects on k_{-1}.

Experimental

Indan-2-one **2** was purchased from the Aldrich Chemical Company, as was α-CD. The other cyclodextrins were obtained from Wacker-Chemie (Munich, Germany) and the γ-CD was purified by recrystallization.[5j]

Enolate formation was carried out by 1:1 stopped-flow mixing of a solution of **2** (200 μmol dm^{-3}) with basic aqueous solutions. The initial experiments were carried out with NaOH solutions, to give [NaOH] = 0.001–0.01 mol dm^{-3}, $I = 0.10$ mol dm^{-3} (NaBr), after mixing. In subsequent experiments with CDs, one syringe of the apparatus contained **2** and a CD, and the other held an aqueous phosphate buffer (0.4 mol dm^{-3}, pH 11.6); no NaBr was added in these experiments. In the case of β-CD, which is the least soluble CD, β-CD was present in both of the syringes.

The first-order production of the enolate of indan-2-one was monitored at 287 nm,[10] using an Applied Photophysics SX17MV Stopped-flow Spectrophotometer, with the observation cell kept at 25.0 ± 0.1 °C. Absorbance traces covering 5–7 half-lives were collected and rate constants were estimated from non-linear least squares fitting of a simple first-order exponential to about 400 data points. The rate constants that were recorded (k_{obs}) were taken from the averages of 7–10 determinations. The constants k_c and K_S in Table 1 were obtained by non-linear least squares fitting of eqn. (3) to k_{obs} values obtained over a range of [CD], as shown in Fig. 1. We observed no significant deviations from eqn. (3) at high [CD] that might be attributed to the onset of 1:2 substrate–CD binding, as found in some of our previous studies of ester cleavage.[5]

Experiments with alcohols as potential inhibitors were carried out after the manner used for comparable studies of ester cleavage,[15] with $[\beta\text{-CD}]_0$ fixed at 5.0 mmol dm^{-3}. Values of k_{obs} were obtained for a range of $[ROH]_0$ (see Fig. 2) and estimation of k_a was carried out by analysis of the variation of k_{obs} with [ROH] in terms of eqn. (7), using K_I for the alcohol[5f] to calculate the actual concentrations of ROH and β-CD, and taking K_S from Table 1. Calculations were carried out in a spreadsheet, as described previously.[15]

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