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THE BINDING OF TRANSITION STATES BY CYCLOMALTO-OLIGOSACCHARIDES

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ABSTRACT

A method of estimating the strength of binding of transition states to catalysts is applied to reactions mediated by cyclomalto-oligosaccharides (cyclodextrins, CDs). The method affords values of the apparent dissociation constant (K_{TS}) of the transition state of the "catalyzed" reaction into that of the "uncatalyzed" reaction and the "catalyst", a CD. Variations in K_{TS} with changes in structure are useful in the study of reactions influenced by CDs, and, in particular instances, the values of log K_{TS} exhibit linear free energy relationships. Examples are presented where the sensitivity (or insensitivity) of the value of K_{TS} (and log K_{TS}) to changes in substrate structure allows a distinction to be made between different modes of binding of the transition state.

INTRODUCTION

The single most important factor in catalysis is the stabilization of the reaction transition state by the catalyst[1]. Hence, any method which provides an estimate of the strength of such stabilization may be useful in the study of catalysis. The simple method devised by Kurz[2] was adopted by enzymologists[3], but largely ignored by chemists. This method has now been applied to reactions mediated by CDs. These molecules[4] form host–guest (inclusion) complexes with a wide variety of organic guests[4,5] and so they can affect the course of organic reactions[4–10].

METHOD

A substrate S reacting via an "uncatalyzed" reaction and a "catalyzed" reaction through a 1:1 complex with a CD (equations *1* and *2*) gives rise to

$$S \xrightarrow{k_u} P \qquad (1)$$

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$$S + CD \underset{K_S}{\rightleftharpoons} S.CD \xrightarrow{k_c} P \qquad (2)$$

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

saturation-type (Michaelis–Menten) kinetics (equation *3*). The resulting rate data can be analyzed[4] to provide the constants k_c and K_S, whereas the rate constant k_u is normally determined directly.

The catalysis (or inhibition) of reactions by CDs is usually discussed in terms of k_c/k_u, K_S, and, less frequently, k_c/K_S. The ratio k_c/k_u is emphasized since it measures the limiting rate acceleration (or retardation) due to the CD. The dissociation constant K_S relates to the strength of the binding of S to CD, but it conveys no information about the mediated reaction. Sometimes, the apparent rate constant for the reaction S + CD → P, $k_2 = k_c/K_S$, is discussed since, like k_{cat}/K_M for enzymes[1], it measures the selectivity of the CD for different substrates.

A more useful quantity is K_{TS} (equation *4*) which is the *apparent* dissociation

$$K_{TS} = \frac{[TS].[CD]}{[TS.CD]} = \frac{k_u.K_S}{k_c} = \frac{k_u}{k_2} \qquad (4)$$

constant of the transition state of the "catalyzed" reaction (here *symbolised* as TS.CD) into the transition state of the normal reaction (TS) and the "catalyst", CD. The derivation of equation *4* follows easily from the application of transition-state theory[2,3] to k_u and k_c. Where saturation kinetics are not observed, $K_{TS} = k_u/k_2$ may be used, with k_2 being obtained from the linear dependence of k^{obs} on [CD]. According to equation *4*, the increase (*or decrease*) in rate is determined[3] by the strength of binding of TS to CD, relative to that of S ($k_c/k_u = K_S/K_{TS}$).

The significance of K_{TS} is illustrated by the energy diagram in Fig. 1, which implies that the relative free energies of species involved in equations *1* and *2* are

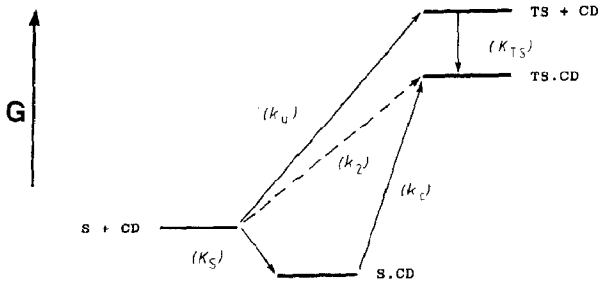


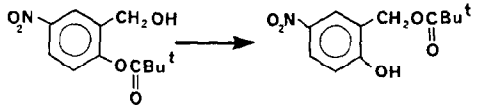
Fig. 1. Relative Gibbs energies for the species involved in the reactions in equations *1* and *2*. For a specified [CD], the energy differences are calculable from the measurable constants k_u, k_c, and K_S (or k_u and k_2), and the derived value of K_{TS}, as indicated.

accessible from the measurable constants k_u, k_c, and K_S (or k_u and k_2). Provided these quantities are measured under the same conditions, K_{TS} (or, more accurately, $\Delta G_0^{\ddagger} = -RT\ln K_{TS}$) gives a measure of the binding energy of the transition state to CD, *whatever the mechanism entailed.* Fig. 1 also emphasizes that it is stabilization of TS by CD which is responsible for any increase in rate; the binding of S is largely irrelevant, except that strong substrate binding must detract from catalysis. This point may be illustrated as follows.

The intramolecular acyl transfer **1** to **2** is catalyzed by αCD but retarded by βCD[11]. As shown by the appropriate constants, below, the difference between the

	k_c/k_u	K_S (mM)	K_{TS} (mM)
αCD	7.3	48	6.6
βCD	0.19	0.96	5.2

two reactions lies in the strength of binding of the substrate (K_S), and *not* of the



1 **2**

transition state (K_{TS}). Binding of the transition state to each CD is similar, but the much stronger binding of the substrate **1** to βCD leads to a decrease in rate ($k_c/k_u < 1$). Apparently, the substrate **1** is bound more tightly in the larger cavity of βCD, so that access to the transition state geometry is made more difficult.

The values of K_{TS} are obtained directly from the rate data *without* any assumptions being made about the mechanisms of the mediated and normal reactions. Therefore, *it should be possible to use variations of K_{TS} with structure as a criterion of mechanism.* For many reactions which are influenced by CDs, variations in K_{TS} may be useful for distinguishing between the different possible modes of binding of the transition states. Furthermore, a comparison of the values of K_{TS} and K_S for different substrates may allow a distinction to be made between the binding of the transition states and their substrates.

In order to emphasize this point, consider the situation where S forms a second complex with CD, in addition to S.CD (equation *2*), with a different geometry and reactivity (equation *5*). Then, equation *3* is replaced by equation *6*, but saturation-type kinetics will still be observed (equation *7*) since the reactions in

$$S + CD \underset{K_S'}{\rightleftharpoons} CD.S' \xrightarrow{k_c'} P \qquad (5)$$

$$k^{obs} = \frac{(k_u.K_S.K_S' + k_c.K_S'.[CD] + k_c'.K_S.[CD])}{(K_S.K_S' + K_S'.[CD] + K_S.[CD])} \quad (6)$$

$$= \frac{(k_u.K_S^{app} + k_c^{app}.[CD])}{(K_S^{app} + [CD])} \quad (7)$$

equations *2* and *5* are kinetically equivalent. The two apparent constants in equation *7* are composite, having the forms:

$$K_S^{app} = K_S.K_S'/(K_S + K_S'); \qquad k_c^{app} = (k_c.K_S' + k_c'.K_S)/(K_S + K_S').$$

From these constants:

$$k_2^{app} = \frac{k_c^{app}}{K_S^{app}} = \frac{k_c}{K_S} + \frac{k_c'}{K_S'}. \quad (8)$$

Equation *8* shows that k_2^{app} reflects the major reaction pathway (equation *2* or *5*), *regardless of the dominant mode of binding of the substrate*, which is reflected in K_S^{app}. If the CD-mediated reaction occurs via equation *2*, then $k_2^{app} = k_c/K_S$, but if it involves the alternative (equation *5*), then $k_2^{app} = k_c'/K_S'$. Correspondingly, $K_{TS} = k_u.K_S/k_c$ or $k_u.K_S'/k_c'$, depending on the dominant reaction pathway. Thus, from variations of K_{TS} and K_S with structure, it should be possible to differentiate between the modes of binding of the transition states and substrates where they are different.

DISCUSSION

The use of the *quasi*-equilibrium constants K_{TS}, calculated from equation *4* or its variants[3], will be illustrated with data taken from the literature and from our own work. In most of the cases, there is a clear choice to be made between two different modes of reaction, or between the modes of binding of the substrate and the transition state.

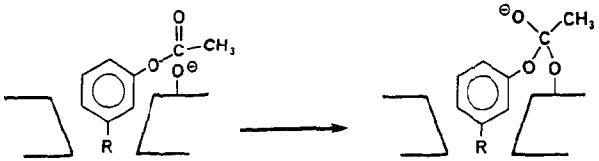
Of all the reactions mediated by CDs, esterolysis has been studied most extensively[4-6,12-25]. Usually, the reaction involves nucleophilic attack of an ionized secondary hydroxyl group of the CD which leads to acyl transfer[4,5]. The resulting acylated CD is normally fairly resistant to hydrolysis so that, overall, the ester hydrolysis is *not* formally catalyzed. Because of the strong covalent interaction of the ester and the CD in the transition state for acyl transfer, low values of K_{TS} can be found (see below). Moreover, they often show strong dependences on the position and size of substituents on the ester. These features are clearly evident in the classic work of Bender and co-workers[12-14], some of whose data are presented in Table I. They found that *m*- rather than *p*-substituted phenyl acetates were superior substrates for ester cleavage by both αCD and βCD in basic aqueous solution[12].

TABLE I

CLEAVAGE OF ARYL ESTERS BY αCD AND βCD IN BASIC AQUEOUS SOLUTION[12]

Substrate	*CD*	k_c/k_u	K_S (mM)	K_{TS} (mM)
(a) X-phenyl acetates				
H	α	27	22	0.81
p-Me	α	3.3	11	3.3
p-Bu^t	α	1.1	6.5	5.9
p-NO_2	α	3.4	12	3.5
m-Me	α	95	17	0.18
m-Cl	α	156	5.6	0.036
m-Et	α	240	11	0.046
m-Bu^t	α	260	2.0	0.0077
m-NO_2	α	300	19	0.063
p-NO_2	β	9.1	6.1	0.67
m-Et	β	89	2.2	0.025
m-NO_2	β	96	8.0	0.083
m-Bu^t	β	250	0.13	0.00052
(b) 4-carboxyphenyl alkanoates				
Me-CO-	α	5.3	150	28
Pr^i-CO-	α	0.68	12	18
Bu^t-CH_2-CO-	α	0.19	1.1	5.8

The transition state for the basic cleavage of phenyl acetate by αCD has a K_{TS} value of 0.81mM [Table I (a)]. Acetates with *p*-substituents have larger values of K_{TS} (weaker TS binding) whereas, for *m*-substituents, the values are lower (stronger TS binding). Thus, the values of K_{TS} support the view that *m*-substituents cause the phenyl group of the ester to adopt a geometry in the cavity of the CD which is more appropriate for formation of the transition state for acyl transfer (**3** → **3'**). In contrast, with *p*-substituents, the phenyl group must be partially outside of the cavity (**4** → **4'**), so that binding to the CD in the transition state is weaker[12–15].



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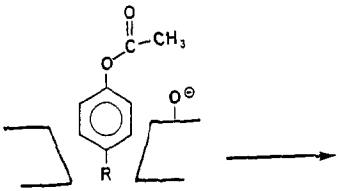
3'



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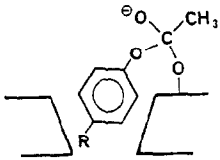


4'

Simple aliphatic compounds with C_2–C_{10} alkyl chains bind increasingly well to CDs, particularly if the end group is reasonably hydrophilic[15,26–28]. Thus, with aryl alkanoates having chains longer than C_1, it is quite possible that inclusion of the alkyl group takes precedence over binding of the aryl group in the initial state *and* in the transition state for ester cleavage. Bender *et al.*[12] studied the esterolysis of three 4-carboxyphenyl esters with different alkanoate chains [see Table I (b)] and found that cleavage of the acetate in aqueous base was accelerated but that of the two longer esters was inhibited. The data clearly show that this situation arises because there is more of an increase in the strength of substrate binding (K_S = 150 → 1.1mM) than of the binding of the transition state (K_{TS} = 28 → 5.8mM), even though the latter improves. The significant variations of K_S and K_{TS} with the variation in the alkanoate chain suggest that, with the two longer esters, both binding of the substrate and the transition state involve inclusion of the alkyl group of the ester in the cavity of the CD.

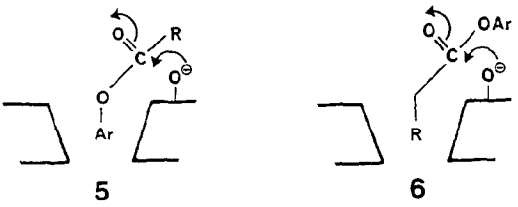
Bonora *et al.*[23] studied the basic cleavage of *p*-nitrophenyl alkanoates (C_2, C_4, C_6, C_8, C_{12}) by αCD and βCD (Table II). The values of K_S diminished with increasing length of the alkanoate chain, implying a change from binding of the aryl group to binding of the alkyl chain of the substrate. Independent spectroscopic evidence[23] suggested that this change occurred beyond C_4. The values of K_{TS}, derived from the kinetic parameters, are similar for the three shorter esters but markedly lower for C_8 and C_{12} (Table II). Thus, a change to binding of the alkyl group apparently also occurs in the transition state for esterolysis.

The cleavage of *m*- and *p*-nitrophenyl alkanoates (C_2–C_6) by CDs has been studied by Du[29]. The idea was to use the normal difference in the behavior of *m*- and *p*-substituted derivatives (see above) as a probe of binding in the transition state (aryl *vs.* alkyl inclusion). If the cleavage reaction proceeds through binding of the aryl group (see **5**), the "normal" distinction between *m*- and *p*-nitrophenyl esters[4,12–15] should be retained. On the other hand, for reaction via inclusion of the alkyl chain (**6**), the kinetic parameters should show a marked, systematic dependence on the length of the alkanoate chain and be relatively independent of the aryl group.

TABLE II

CLEAVAGE OF *p*-NITROPHENYL ALKANOATES BY CDs IN BASIC AQUEOUS SOLUTION[23]

Acyl group	*αCD*			*βCD*		
	k_c/k_u	K_S (mM)	K_{TS} (mM)	k_c/k_u	K_S (mM)	K_{TS} (mM)
C_2	3.2	10.5	3.3	12.2	6.5	0.53
C_4	1.6	4.8	3.0	8.2	3.9	0.48
C_6	2.5	2.0	0.80	5.8	2.3	0.40
C_8	3.6	0.98	0.27	9.8	1.9	0.19
C_{12}	10.6	0.37	0.035	67	0.75	0.011



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The results for *p*-nitrophenyl esters (Table III) were comparable to those reported earlier[23]. The accelerations in rate (k_c/k_u) first decreased and then increased with the increase in the length of the alkyl chain, and, from the propanoate ester onwards, the values of K_{TS} decreased regularly (see below), consistent with progressively stronger binding of the alkyl chain in the transition state (**6**). In contrast, the values of K_{TS} for the *m*-nitrophenyl esters (Table III) showed little dependence on chain length, at least to C_6, suggesting that reaction through binding of the aryl group (**5**) is retained for these substrates.

The binding of guests to CD hosts in aqueous solution is governed by the size and hydrophobicity of the guests[4,5,15,26–28,30]. The sizes of *n*-alkyl chains increase linearly with the number of carbons (N), and so do measures of their hydrophobicity[31–33]. Accordingly, it is reasonable to expect that values of $-\log K_S$ and $-\log K_{TS}$, which are linear in free energy, should increase in a regular manner with N where the binding of *n*-alkyl chains is dominant. Such correlations are shown by the binding of *n*-alkyl alcohols (C_1–C_8) to both αCD and βCD[28] (equations *9* and *10*), and by other alkyl-bearing substrates[15,26,27].

$$\alpha\text{CD:} \quad -\log K_S = (0.54 \pm 0.02)N - (0.34 \pm 0.12);\ r = 0.994 \qquad (9)$$

$$\beta\text{CD:} \quad -\log K_S = (0.55 \pm 0.02)N - (1.03 \pm 0.09);\ r = 0.997 \qquad (10)$$

The *p*-nitrophenyl alkanoates beyond the acetate [C_3–C_6 (ref. 29), C_8, and C_{12} (ref. 23)] show good correlations for binding of the substrates to αCD *and* for binding of the transition states for ester cleavage (equations *11* and *12*).

TABLE III

CLEAVAGE OF ARYL ALKANOATES BY αCD[a] IN AQUEOUS BASE[29]

Acyl group	p-*Nitro*			m-*Nitro*		
	k_c/k_u	K_S (*m*M)	K_{TS} (*m*M)	k_c/k_u	K_S (*m*M)	K_{TS} (*m*M)
C_2	2.8	10	3.6	290	25	0.087
C_3	1.7	12	6.0	110	6.5	0.057
C_4	1.9	5.0	2.6	110	5.4	0.050
C_5	2.1	3.4	1.6	70	4.1	0.058
C_6	3.1	2.9	0.97	82	3.5	0.042

[a]Similar results have been obtained for βCD.

$$\alpha\text{CD:} \quad -\log K_S = (0.15 \pm 0.01)N + (1.72 \pm 0.06); r = 0.992 \qquad (11)$$

$$\alpha\text{CD:} \quad -\log K_{TS} = (0.25 \pm 0.01)N + (1.56 \pm 0.05); r = 0.998 \qquad (12)$$

The slopes of the lines indicate a greater sensitivity of the values of K_{TS} to the alkyl chain length, presumably due to more rigid requirements of the partial covalent binding in the transition state for acyl transfer. Moreover, the strong correlation (and slope) of equation *12* indicates that alkyl group binding in the transition state (**6**) is important from the propanoate to the dodecanoate ester.

The values of K_S for *m*-nitrophenyl esters (C_3–C_6) also correlate with N (equation *13*), whereas the values of K_{TS} show almost no dependence (equation *14*). It appears, therefore, that cleavage of the *m*-nitrophenyl alkanoates via

$$\alpha\text{CD:} \quad -\log K_S = (0.093 \pm 0.007)N + (1.91 \pm 0.03); r = 0.995 \qquad (13)$$

$$\alpha\text{CD:} \quad -\log K_{TS} = (0.037 \pm 0.028)N + (4.12 \pm 0.13); r = 0.687 \qquad (14)$$

binding of the aryl group (**5**) is so superior that it is maintained (at least to C_6), even though the ester substrates most probably bind to αCD through their alkyl chains (equation *13*).

The markedly different behaviours of the *m*- and *p*-nitrophenyl esters are clearly seen in Fig. 2, which shows the data corresponding to equations *12* and *14*.

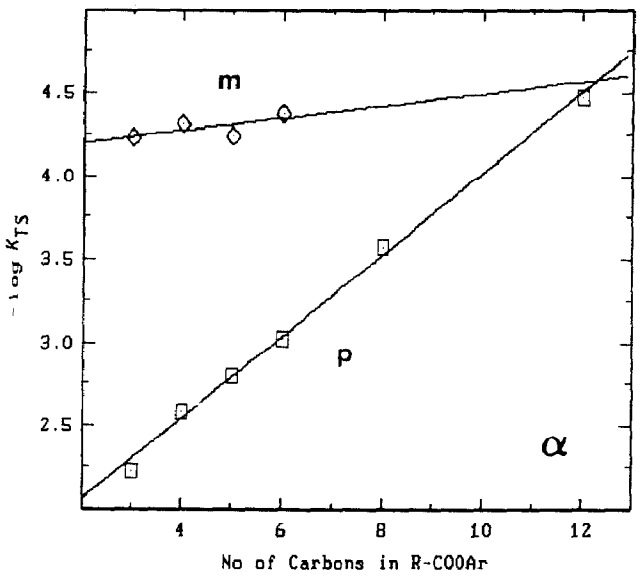


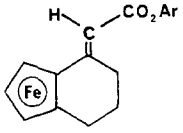
Fig. 2. Variation of log K_{TS} with acyl chain-length for the cleavage of *m*- and *p*-nitrophenyl alkanoates (**m** and **p**). Such correlations, where they exist, can be considered as linear free energy relationships (see text).

If extrapolation of equation *14* is valid, then *m*-nitrophenyl alkanoates must have acyl chains of 12 or more carbon atoms for there to be a switch from binding of the aryl group to binding of the alkyl group in the transition state for ester cleavage (from **5** to **6**).

The equations *9–13* are, in essence, linear free energy relationships. This arises because hydrophobicity parameters, which are linear in free energy[31–33], are linear in N for *n*-alkyl compounds. Also, where both $-\log K_S$ and $-\log K_{TS}$ are linear in N, as with equations *11* and *12*, these quantities are, of course, related linearly to each other.

2-Carboxy-5-chlorophenyl acetate (4-chloroaspirin) is cleaved more easily by αCD than is its 4-chloro isomer (5-chloroaspirin)[22], in line with the behavior of other *m*- and *p*-substituted phenyl acetates[12,15] (see above). This distinction between isomers is also present[34] for longer chain homologues of the chloroaspirins, at least to C_6. For ester cleavage by either αCD or βCD, the values of K_S and K_{TS} show little or no variation with increasing chain length, strongly suggesting that both substrates *and* transition states for the 4- *and* 5-chloro series of alkanoates bind preferentially with their aryl groups (**5**). These results and conclusions are in sharp contrast to those for the *m*- and *p*-nitrophenyl esters, discussed above.

The "best" substrate found by Bender and co-workers[12] was *m-tert*-butylphenyl acetate, undergoing cleavage by βCD. For these reactants, $k_c/k_u = 250$ (not unusually large) and $K_{TS} = 5.2 \times 10^{-7}$M, which is much lower than the values for other simple aryl acetates [Table I (a)]. Subsequently, Breslow's group[19–21], using designed ferrocene-based esters, obtained spectacular rate increases, with k_c/k_u ranging up to 6 million. These large accelerations are associated with very low values of K_{TS}, as low as 10^{-9}M, the values of K_S being in the mM range.



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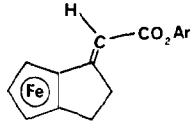

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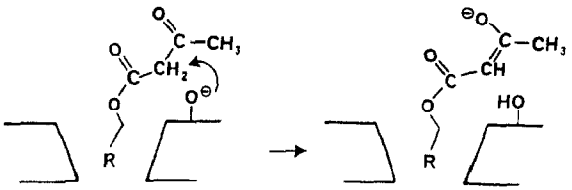
	$K_S = 3.8$	5.7	(mM)
	$k_c/k_u = 3\ 200\ 000$	5 900 000	
	$K_{TS} = 1.2 \times 10^{-9}$	9.7×10^{-10}	(M)
enantiomer:	$K_S = 4.6$	4.7	(mM)
	$k_c/k_u = 160\ 000$	95 000	
	$K_{TS} = 2.9 \times 10^{-8}$	4.9×10^{-8}	(M)
	selectivity = 20	62	

Also, for the esters **7** and **8** reacting with βCD, large enantioselectivities of 20 and 60 were found[20,21]. In both cases, the values of K_{TS} and K_S show that these selectivities arise principally from differences in the strengths of binding of the diastereomeric transition states, and *not* of the enantiomeric substrates.

For some ester cleavages, the anion of CD functions not as a nucleophile but as a general base, assisting the attack of water in a truly catalytic process[16,17]. Also, anions of CDs (pK_as ca. 12.2)[35,36] may function as simple bases towards acidic substrates included in their cavities. For example, CDs catalyze the deprotonation of long-chain β-keto esters in basic aqueous dimethyl sulfoxide[37]. Similar *true* catalysis was found[38] for small β-keto esters reacting with αCD and βCD in aqueous base; the results for αCD are summarized in Table IV.

For the esters R–$COCH_2COOEt$, changes in the alkyl group R cause little variation in the kinetic parameters and the values of K_{TS} are very similar, with the possible exception of R = Pr^i. A similar value of K_{TS} was found for 2-ethoxycarbonylcyclopentanone. In contrast, for changes in the alkoxyl group ($MeCOCH_2CO_2R$ or $EtCOCH_2CO_2R$), larger variations of K_{TS} were found. With methyl esters (R–$COCH_2CO_2Me$), saturation-type kinetics were not observed and so the binding of these esters in the initial state must be weak. For ethyl and allyl esters, the values of K_S and K_{TS} decrease with the size of the alkoxyl group. Taken as whole, the results suggest that the catalytic deprotonation involves a transition state in which the alkoxyl chain, rather than the acyl chain, is bound in the cavity of the CD (**9** rather than **10**).



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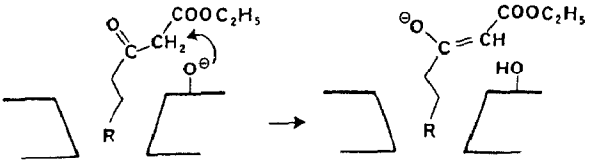

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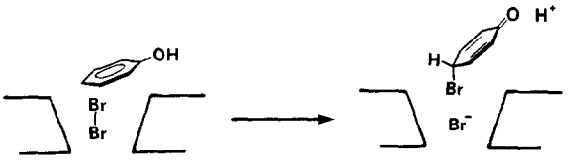
Reactions which require two substrate molecules in order to reach the transition state may be treated in a manner[3] analogous to that in equation *4*. The value of K_{TS} is most easily obtained from the ratio of the second-order rate constant for the uncatalyzed reaction and the third-order rate constant for the catalyzed reaction:

$$S_1 + S_2 \xrightarrow{k_{2u}} P \qquad S_1 + S_2 + CD \xrightarrow{k_{3c}} P \tag{15}$$

$$K_{TS} = k_{2u}/k_{3c} \tag{16}$$

This situation arises in the bromination of phenols and phenoxide ions, which are catalyzed by αCD[39]. For 15 substrates, with a range of reactivity of 40 million, the values of K_{TS} (Table V) varied only from 0.07 to 0.8mM, and showed no clear correspondence to K_S for the substrates. This insensitivity of K_{TS} to the nature and position of the substitutent is strong evidence that the transition state of the CD-catalyzed process develops from a configuration in which the phenolic moiety is outside the cavity of the CD while bromine is inside (**11**).



11 **12**

As an alternative approach to probing the structure of the transition state in **11** → **12**, the debrominations of 4-alkyl-4-bromo-2,5-cyclohexadienones[40] (see **13**, below) were also studied. These reactions, which are strongly catalyzed by αCD[41],

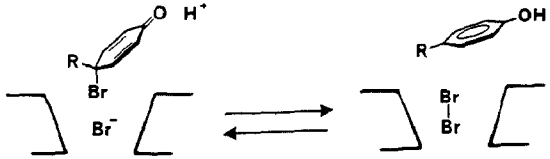
TABLE IV

CONSTANTS FOR THE DEPROTONATION OF β-KETO ESTERS BY αCD[a] IN BASIC AQUEOUS SOLUTION[38]

Substrate	k_c/k_u	K_S (mM)	K_{TS} (mM)
(a) R–$COCH_2CO_2Et$:			
R = Me	7.5	3.1	0.41
R = Et	6.7	1.8	0.26
R = Pr	12	3.4	0.29
R = Pr^i	17	1.1	0.064
2-Ethoxycarbonylcyclopentanone	18	11	0.61
(b) $MeCOCH_2CO_2$–R			
R = Me	[b]	[b]	5.8
R = Et	7.5	3.1	0.41
R = allyl	8.4	0.22	0.026
(c) $EtCOCH_2CO_2$–R			
R = Me	[b]	[b]	3.8
R = Et	6.7	1.8	0.26

[a]The values for βCD are similar, but the values of K_S are higher (weaker substrate binding) and those of k_c/k_u are lower, so that the values of K_{TS} are also higher (weaker transition-state binding). [b]Saturation kinetics were *not* observed. Therefore, K_{TS} was calculated from k_2/k_u, where k_2 was obtained from the linear dependence of k^{obs} on [CD].

were chosen to serve as reasonable models for the reverse of the catalyzed brominations just discussed. The values of K_{TS} for alkyl groups of different size and shape fall in the narrow range 0.06–0.12mM (Table VI), suggesting that CD-catalyzed debromination takes place with the dienone moiety outside of the cavity of the CD and bromide ion inside (**13**). This conclusion requires that the reverse reaction (*ipso* bromination) occurs from CD-complexed bromine reacting with free *p*-alkylphenol (**14**). Thus, two quite distinct studies lead to the same description of the common transition state for bromination and debromination (**13** ⇌ **14**). This same description was arrived at earlier[39,41], using other, more detailed arguments, not involving the use of K_{TS} values.



13 **14**

An interesting example[42] of debromination catalyzed by αCD is that of the dienone **15**, which is also subject[43] to intramolecular general acid catalysis by the carboxyl group (**15** → **16**). This reaction was chosen for study in order to see how two different forms of catalysis interact, namely, constructively, passively, or destructively. Enzymes achieve their remarkable efficacy by combining several

TABLE V

CONSTANTS[39] FOR THE ATTACK OF BROMINE ON PHENOLS AND PHENOXIDE IONS, CATALYZED BY αCD

Substrate	k_2 ($M^{-1}.s^{-1}$)	k_3 ($M^{-2}.s^{-1}$)	K_S (mM)	K_{TS} (mM)
Phenols				
H	4.1×10^5	3.5×10^9	50	0.12
2-Me	1.5×10^6	2.2×10^{10}	4.3	0.068
2,6-diMe	1.2×10^6	1.2×10^{10}	15	0.10
2-Br	1.0×10^4	6.7×10^7	52	0.15
4-Me	6.6×10^5	2.4×10^9	83	0.28
4-Bu^t	5.9×10^5	8.9×10^8	7.0	0.66
4-Br	3900	8.5×10^6	1.4	0.46
4-CO_2Et	1600	3.4×10^6	4.8	0.47
4-CN	160	4.4×10^5	7.1	0.36
Phenoxides				
2-NO_2	1.6×10^9	5.7×10^{12}	~40	0.28
2-Br	6.2×10^9	7.9×10^{12}	~110	0.78
3-NO_2	4.2×10^9	2.8×10^{13}	4.2	0.15
4-NO_2	1.2×10^9	4.8×10^{12}	0.47	0.25
4-Br	5.4×10^9	2.0×10^{13}	1.2	0.27
4-CN	3.1×10^9	5.8×10^{12}	1.6	0.53

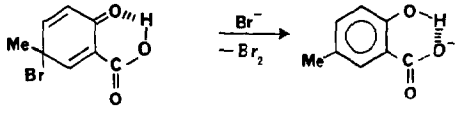
TABLE VI

CONSTANTS[41] FOR THE CATALYSIS OF DEBROMINATION OF 4-ALKYL-4-BROMO-2,5-CYCLOHEXADIENONES BY αCD

Alkyl	k_c/k_u[a]	K_S (mM)	K_{TS} (mM)
Me	78	4.8	0.062
Et	39	2.9	0.074
Pr^i	23	2.4	0.11
Pr	12	0.75	0.063
Bu^t	28	2.3	0.083
3,4-diMe	29	3.6	0.12
Me, 2-COOH (**15**)[42]	170	15	0.088

[a]The values of k_c/k_u are for the apparent reaction of complexed substrate with bromide ion. For the mechanism preferred (**13** → **14**), the values are 2400–4600 (ref. 41), the value for **15** being 3400 (ref. 42). For a fuller discussion, see the references cited.

catalytic effects in one process[1], and so it is of interest to study chemical reactions in which more than one type of catalysis operates.



15 **16**

The kinetic parameters for the catalysis of the debromination of **15** to **16** by αCD are similar to those for other *ipso*-dienones[42], even though **15** is much more reactive[40]. In particular, the value of K_{TS} of 0.088mM is in the middle of the range of the other values (Table VI). Again, this finding is consistent with the transition state for debromination having the dienone moiety outside of the cavity of the CD (**13** → **14**). Also, it appears that the two forms of catalysis, which give a combined rate enhancement of *~12 million*, operate more or less independently[42].

CONCLUSIONS

Values of K_{TS} can provide insights into the structures of the transition states of reactions mediated by cyclodextrins. In particular, variations of K_{TS} with structure may be used to distinguish between different possible modes of binding of the transition state. These variations may be cast in the form of linear free energy relationships (−log K_{TS} *vs.* some appropriate parameter). Also, correlations between log K_{TS} and log K_S may provide a means of probing the relation between the binding of transition states and substrates*.

*The approach used in this paper, as applied to enzymes, has been reviewed critically by Kraut[44].

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