Chain Length Effects in the Cleavage of Aryl Esters by Cyclodextrins. Different Transition States for *m*- and *p*-Nitrophenyl Alkanoates

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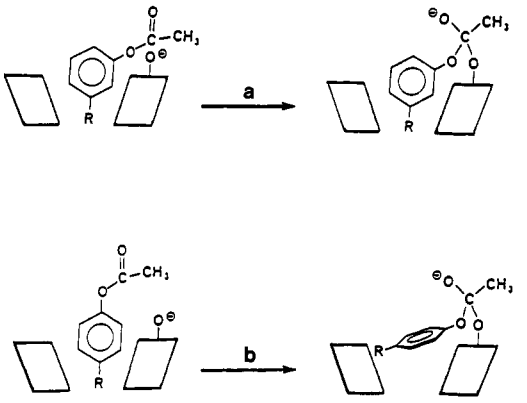
The kinetics of cleavage of *m*- and *p*-nitrophenyl esters (acetate, propanoate, butanoate, pentanoate, and hexanoate) in a basic aqueous phosphate buffer containing α- or β-cyclodextrin (α- or β-CD) have been measured. For these two series of esters the *m*-nitro derivatives undergo more efficient cleavage than their *p*-nitro isomers, indicating that the former react via a transition state in which the aryloxy moiety is included in the CD cavity, even though substrate binding probably occurs through the alkyl group. For the *p*-nitrophenyl esters kinetic parameters vary significantly with the length of the alkanoate chain, and in a manner that suggests that substrate binding *and* transition-state binding both involve inclusion of the alkyl moiety. In contrast to the above, kinetic parameters for the cleavage of 2-carboxy-4(or 5)-chlorophenyl esters by α- and β-CD show little or no variation with the chain length of the alkanoate, implying that both series of esters react solely by aryloxy group inclusion. The present studies illustrate the usefulness of the pseudo constants pK_{TS} (= $-\log K_{TS}$), where K_{TS} is the *apparent* dissociation constant of the transition state of the CD-mediated reaction into the transition state of the normal reaction and CD. The variation of these constants with structure can be a useful probe of mechanism, particularly with regard to the mode of binding of transition state of the CD-mediated reaction.

Introduction

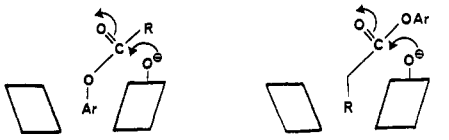
In basic aqueous solution cyclodextrins[1,2] cleave phenyl acetates by acyl transfer from the ester to an ionized hydroxyl group of the cyclodextrin.[1,3-7] The reaction takes place within an inclusion complex in which the phenyl group of the ester resides in the hydrophobic cavity of the cyclodextrin (CD).[1-7] As a result, the efficiency of the ester cleavage, relative to that by hydroxide ion, is generally greater for meta than for para substituents since the former orient their phenyl groups within the CD cavity in geometries that are more suitable for acyl transfer (see Scheme I, a and b).[3-7]

The initial object of the present study was to see how the different reactivities of meta- and para-substituted phenyl esters are affected by increases in the lengths of their acyl chains. At the same time, it was hoped that the normal reactivity difference could be exploited to probe the modes of binding and cleavage of simple aryl alkanoates. With these substrates, both of the groups flanking the ester function are hydrophobic, and it was not readily apparent which of the groups (aryl or alkyl)[8] would bind preferentially in the cavity of the CD, either in the initial state or in the transition state for ester cleavage. In particular, we were interested in seeing how alkyl binding[8] affects reactivity, since this aspect has not been widely studied.[1,7]

Scheme I



Our working hypothesis can be appreciated by referring to the structures 1 and 2. If ester cleavage proceeds



1 2

through a transition state in which the aryl moiety is bound in the CD cavity (1), then the usual distinction between meta- and para-substituted derivatives[3] should be evident in the kinetic parameters of the reaction. On the other hand, if esterolysis involves a transition state with the alkyl chain included in the CD cavity (2), then the meta/para distinction should be largely absent and the parameters should mainly reflect the length of the alkyl group.

After our studies were begun, we became aware of a recent report[10] on the cleavage of a series of *p*-nitrophenyl alkanoates (acyl = C2, C4, C6, C8, C12) by α- and β-cyclodextrins[1,2] in basic solution. Spectroscopic evidence was presented that for longer acyl chains (>C6 for α-CD and >C4 for β-CD), binding of the alkyl group of the ester substrate takes precedence over that of its aryl group. Also, from kinetic behavior, it was concluded that the

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(2) (a) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. (b) Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds. *Inclusion Compounds*; Academic Press: London, England, 1984; Vol. 2, Chapter 8; Vol. 3, Chapters 12 and 13. (c) Stoddart, J. F.; Zarzycki, R. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 515.

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(7) Matsui, Y.; Nishioka, T.; Fujita, T. *Top. Curr. Chem.* **1985**, *128*, 61.

(8) The binding of alkyl chains is documented. For example, cyclodextrins form inclusion complexes with linear alcohols, alkylphenols, acylphenols,[7] and medium length surfactants.[9]

(9) Satake, I.; Ikenoue, T.; Takeshita, T.; Hayakawa, K.; Meda, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2746. Satake, I.; Yoshida, S.; Hayakawa, K.; Meda, T.; Kusumoto, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3991.

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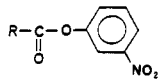
0022-3263/90/1955-3603$02.50/0

transition state for ester cleavage changes to one in which the alkyl group is included in the CD cavity.[10] However, it is by no means certain that the changes in substrate binding and in transition-state binding (i.e., a change from 1 to 2) occur at the same chain length. As will be discussed more fully later, ester cleavage could take place from a minor, less favorable substrate·CD complex, if it is sufficiently reactive.

It was against this background that the present studies were carried out. We hoped that a comparison of the behavior of two series of meta- and para-substituted phenyl esters (3 vs 4 and 5 vs 6) might help us to distinguish between the mode of binding of the substrates and that of the transition states for ester cleavage.



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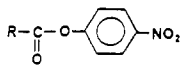

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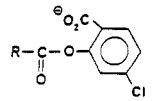

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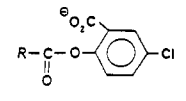

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acetate (C2), propanoate (C3), butanoate (C4), pentanoate (C5), hexanoate (C6)

Results and Discussion

We have measured rate constants for the cleavage of *m*- and *p*-nitrophenyl *n*-alkanoates 3 and 4 by α- and β-cyclodextrin[11] in a basic aqueous phosphate buffer. Similarly, we have examined the behavior of the 2-carboxychlorophenyl esters 5 and 6 with α- and β-CD, since earlier work in this laboratory has shown that 2-carboxy-5-chlorophenyl acetate (4-chloroaspirin) is cleaved much more readily by α-CD than its 4-chloro isomer.[6] In all cases, except one, simple saturation-type kinetics were observed (Tables S1–S4, supplementary material). In the exceptional case, that of *p*-nitrophenyl propanoate reacting with α-CD, there appears to be productive 1:1 *and* nonproductive 2:1 binding, similar to the behavior we found recently for some other aryl alkanoate esters.[12] Before presenting these results and discussing them in detail, we first outline the methodology of our approach.

Methodology. A substrate (S) that undergoes an "uncatalyzed" reaction (eq 1) and also reacts via a complex with a CD (eq 2) exhibits saturation kinetics[1] (eq 3). By

$$S \xrightarrow{k_u} P \tag{1}$$

$$S + CD \underset{K_S}{\rightleftharpoons} S{\cdot}CD \xrightarrow{k_c} P \tag{2}$$

$$k^{obsd} = \frac{(k_u{\cdot}K_S + k_c{\cdot}[CD])}{(K_S + [CD])} \tag{3}$$

an appropriate analysis of the dependence of k^{obsd} on [CD], one can obtain the constants k_c and K_s.[3,6] For the most part, discussions of catalysis by CDs are given in terms of k_c/k_u, which measures the rate acceleration or retardation, and of K_S, which indicates the strength of the substrate binding. Less often, the quantity $k_2 = k_c/K_S$ is discussed. It is the apparent second-order rate constant for S + CD → P, and a measure of the selectivity of the CD for the substrate, under the reaction conditions.[3,6] In most cases where k_c is pH dependent, as here, then so is k_2. Much more useful, we believe,[13] is the quantity K_{TS} (eq 4).[14,15]

$$K_{TS} = \frac{[TS]{\cdot}[CD]}{[TS{\cdot}CD]} = \frac{k_u{\cdot}K_S}{k_c} = \frac{k_u}{k_2} \tag{4}$$

This quantity, which does not depend on pH when k_c and k_u have the same dependence, is the *apparent* dissociation constant of the transition state of the catalyzed reaction (symbolized as TS·CD) into the transition state of the normal reaction (TS) and the "catalyst", here CD. It provides a direct measure of the stabilization of the transition state by the "catalyst".[13-15] Moreover, since eq 4 is derived without any assumptions being made about reaction mechanisms, *variations of K_{TS} with structure may be used as a probe of mechanism.*[13]

If the substrate also forms another complex with CD that has a different geometry and reactivity (eq 5), then eq 3 must be replaced by eq 6. Saturation kinetics should still be observed (eq 7), since the processes in eqs 2 and

$$S + CD \underset{K_S'}{\rightleftharpoons} CD{\cdot}S' \xrightarrow{k_c'} P \tag{5}$$

$$k^{obsd} = \frac{(k_u{\cdot}K_s{\cdot}K_s' + k_c{\cdot}K_s'{\cdot}[CD] + k_c'{\cdot}K_s{\cdot}[CD])}{(K_s{\cdot}K_s' + K_s'{\cdot}[CD] + K_s{\cdot}[CD])} \tag{6}$$

$$= \frac{(k_u{\cdot}K_s^{app} + k_c^{app}{\cdot}[CD])}{(K_s^{app} + [CD])} \tag{7}$$

5 are kinetically equivalent, but the apparent constants in eq 7 are composite, having the forms:

$$K_s^{app} = K_s{\cdot}K_s'/(K_s + K_s')$$

$$k_c^{app} = (k_c{\cdot}K_s' + k_c'{\cdot}K_s)/(K_s + K_s')$$

From these

$$k_2^{app} = \frac{k_c^{app}}{K_s^{app}} = \frac{k_c}{K_s} + \frac{k_c'}{K_s'} \tag{8}$$

The above analysis shows that k_2^{app} should reflect the dominant catalyzed pathway (eq 2 or eq 5), regardless of the principal mode of substrate binding. More precisely, if the catalysis proceeds via the pathway represented by eq 2, then $k_c/K_s \gg k_c'/K_s'$ and $k_2^{app} = k_c/K_s$, whereas if the other reaction pathway (eq 5) is dominant ($k_c/K_s \ll k_c'/K_s'$), then $k_2^{app} = k_c'/K_s'$. Likewise, from eq 4, $K_{TS} = k_u{\cdot}K_s/k_c$ or $k_u{\cdot}K_s'/k_c'$, depending on the pathway that is followed. Therefore, variations of K_{TS} (or k_2^{app}) and K_s^{app} with substrate structure may be used to differentiate between the mode of binding of the transition state, as opposed to that of the substrate.[13]

The binding of organic substrates to cyclodextrins is largely determined by their hydrophobicity and size.[1,2,7] For linear aliphatic molecules, both of these properties increase linearly with the number of carbons (*N*) in the alkyl chain. Obviously, the "size" of *n*-alkyl chains increases monotonically with *N*, but so also do several measures of their hydrophobicity.[16-18] Such is the case

(11) α-Cyclodextrin (cyclohexaamylose) has 6 glucose units joined in a torus whereas β-cyclodextrin (cycloheptaamylose) has 7 units. Thus, the sizes of their cavities differ in width, but not in depth.[1,2]

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(15) The derivation of eq 4 follows from the application of transition-state theory to k_u and k_c.[14] Despite its considerable potential for describing the binding of transition states, the quantity K_{TS} has not been widely used by physical organic chemists.

Table I. Chain Length Dependence of the Binding of *n*-Alkyl Compounds to α- and β-Cyclodextrin. Correlations between pK_S and N (cf. Figure 1 and eq 9)[a]

substrate	CD	alkyls	slope	s.d.	r	ref
ROH	α	C1–C6	0.593	0.026	0.996	*b*
	β	C1–C7	0.571	0.010	0.999	*b*
m-RPhOH	α	C1–C4	0.580	0.054	0.991	*c*
	β	C1–C4	0.602	0.029	0.998	*c*
p-RPhOH	α	C1–C4	0.587	0.019	0.999	*c*
	β	C1–C4	0.552	0.035	0.996	*c*
m-RPhOAc	α	C1–C4	0.465	0.011	0.999	*c*
	β	C1–C4	0.495	0.029	0.997	*c*
p-RPhOAc	β	C1–C4	0.371	0.024	0.996	*c*
RSO_3^-	α	C5–C8	0.274	0.029	0.989	*d*
	β	C5–C8	0.408	0.016	0.998	*d*
RCO_2-*m*-NO_2Ph	α	C2–C5	0.093	0.006	0.995	*e*
	β	C2–C5	0.157	0.008	0.997	*e*
RCO_2-*p*-NO_2Ph	α	C2–C5	0.202	0.050	0.944	*e*
	β	C2–C5	0.194	0.022	0.988	*e*

[a] In aqueous solution, at 25 °C. The slope, its standard deviation (s.d.), and correlation coefficient (r) are from the least-squares analysis of pK_S vs N. [b] From data in ref 21. [c] From data in ref 7. [d] From data in ref 9. [e] This work.

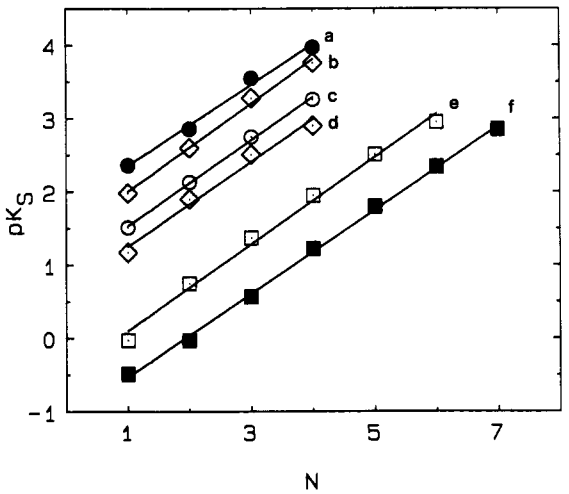

Figure 1. Chain length dependence of pK_S for (a) *p*-alkylphenols with β-CD; (b) *m*-alkylphenols with β-CD; (c) *p*-alkylphenols with α-CD; (d) *m*-alkylphenols with α-CD; (e) alkanols with α-CD; (f) alkanols with β-CD. N is the number of carbons in the alkyl group of the substrate. Part of the data presented in Table I.

for "macroscopic" and "microscopic" hydrophobicity parameters,[17,18] as well as for the Gibbs energies of transfer of aliphatic compounds from various organic media to water.[16,17] It is not unreasonable, therefore, to find that values of $pK_S = -\log K_s$ ($= \Delta G^0_S/2.303RT$) for alkyl-substituted derivatives increase with N in a roughly linear fashion, for N up to ~7.[19] As seen in Table I, good correlations, of the form of eq 9, exist for the complexation

$$\text{R-OH}/\alpha\text{-CD:} \quad pK_S = 0.59N - 0.49;\ r = 0.996 \quad (9a)$$

$$\text{R-OH}/\beta\text{-CD:} \quad pK_S = 0.57N - 1.10;\ r = 0.999 \quad (9b)$$

of both α-CD and β-CD with *n*-alkanols, *m*- and *p*-alkylphenols (and their acetates), and alkanesulfonate ions. Some examples are plotted in Figure 1.

In view of these observations, it is reasonable to look for correlations of pK_s *and* of pK_{TS} ($= -\log K_{TS}$) with N as a means of probing the inclusion of the *n*-alkyl chains[13] of the present esters (**3**–**6**). Such correlations, where they exist, may be considered as linear free energy relationships (LFERs), since the Gibbs energies for the transfer of *n*-alkyl compounds from organic media to water are linear in N.[16,17]

Nitrophenyl Alkanoates. The constants k_u, k_c, and K_S, obtained for the esters **3** and **4**, are collected in Table II, together with the derived quantitites k_2 and K_{TS}. Also presented there are some of the constants derived from the earlier study.[10] Broadly speaking, the kinetic parameters indicate that the difference in reactivity between the *m*- and *p*-nitrophenyl esters is maintained throughout the series acetate to hexanoate (C2 to C6), with both α-CD and β-CD.

It will be noted from the values of k_u in Table II (and later in Table III) that the longer esters (>C3) are inherently less reactive than the acetates and propanoates. This behavior, which is quite normal, is due to steric hindrance of the nucleophilic attack on the ester carbonyl.[22] However, for longer *p*-nitrophenyl alkanoates, beyond C3 and up to at least C12, the rate constants for basic hydrolysis are all much the same, as long as the effects of hydrophobic aggregation are absent.[23]

For the *p*-nitrophenyl alkanoates **4** (C2 to C6) reacting with α-CD the rate accelerations are modest (k_c/k_u = 2–3), whereas for the isomers **3** these ratios fall in the range 70–300. Likewise, the second-order rate constants k_2 for **3** are much larger (500–1000 M^{-1} s^{-1}) than for **4** (20–50 M^{-1} s^{-1}) (Table II, A). These differences in reactivity are also clearly expressed the values of K_{TS}, which indicate that the binding of the transition states for cleavage of the *m*-nitrophenyl esters by α-CD is 20–40 times stronger. In contrast, substrate binding (see K_S values) in the two series is quite similar.

Similar trends are seen in the kinetic parameters for cleavage by β-CD (Table II, B), although the differences between the two series of esters are not as large. As clearly shown by the values of K_{TS}, this situation arises because the binding of the transition states to β-CD for the *p*-nitrophenyl esters is stronger, whereas that for the *m*-nitro isomers is weaker, relative to the transition-state bindings to α-CD. In each series the values of k_2 are almost constant for the esters C2 to C6, with the *m*-nitrophenyl esters being 3–4 times more reactive. Likewise, the values of K_{TS} show little change, although there is a downward trend with increasing chain length. Thus, from our data alone for the C2 to C6 esters reacting with β-CD, there is little sign of a convergence of the kinetic parameters for the two series of esters that would clearly indicate that aryl inclusion (**1**) gives way to alkyl inclusion (**2**) in the transition state.

Overall, it is clear that the *m*-nitrophenyl alkanoates **3** react via a transition state in which the aryl group is included in the cavity of the CD (**1**). Apparently, the effi-

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(19) Beyond about C7 or C8 the increase in pK_S tends to level off, due to the finite depths of the CD cavities.[1,2] This "saturation" effect is clearly seen with alkanesulfonate ions[9] and also with carboxylate ions.[20] The available data for alcohols[7,21] extend only to C8 so that the onset of levelling is only just discernible. With the alkylphenols and their acetates the levelling seems to start at C5,[7] presumably due to the contribution of the phenyl group.

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Table II. Constants for the Cleavage of Nitrophenyl Esters 3 and 4 in the Presence of Cyclodextrins[a]

acyl	K_S, mM	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u	k_2, M^{-1} s^{-1}	K_{TS}, mM
			(A) α-Cyclodextrin			
m-nitro						
C2	25	0.086	25	290	1000	0.086
C3	6.5	0.040	4.5	110	690	0.059
C4	5.4	0.029	3.2	110	590	0.049
C5	4.1	0.028	2.0	71	490	0.058
C6	3.5	0.024	2.0	83	570	0.042
p-nitro						
C2	10	0.096	0.27	2.8	27	3.6
C3[b]	12	0.099	0.20	1.7	17	6.0
C4	5.0	0.058	0.11	1.9	22	2.6
C5	3.4	0.045	0.093	2.1	27	1.6
C6	2.9	0.049	0.15	3.1	52	0.94
C8[c]	0.98	*d*	*d*	3.6	*d*	0.27
C12[c]	0.37	*d*	*d*	11	*d*	0.034
			(B) β-Cyclodextrin			
m-nitro						
C2	12	0.086	5.3	62	440	0.19
C3	5.2	0.040	1.7	43	330	0.12
C4	3.7	0.027	0.91	34	250	0.11
C5	2.4	0.028	0.66	24	280	0.10
C6	1.8	0.023	0.61	27	340	0.067
p-nitro						
C2	7.8	0.096	0.78	8.1	100	0.96
C3	5.2	0.099	0.47	4.7	90	1.10
C4	2.7	0.058	0.27	4.7	100	0.57
C5	2.0	0.047	0.18	3.8	90	0.53
C6	1.3	0.049	0.18	3.7	140	0.35
C8[c]	1.9	*d*	*d*	9.8	*d*	0.19
C12[c]	0.75	*d*	*d*	67	*d*	0.011

[a] At 25 °C, in 0.2 M phosphate buffer (pH 11.7). [b] This ester undergoes 1:1 and 2:1 binding (see Experimental Section). [c] Based on the data of Bonora et al.[10] [d] Not comparable because of the different media involved (see Experimental Section).

ciency of this mode of ester cleavage is so superior for *m*-nitrophenyl esters that the alternative of reaction through a transition state with alkyl group binding (**2**) cannot compete, at least for acyl groups in the range C2 to C6. It *may* be competitive for much longer chains, as discussed later.

The situation is less clear for the *p*-nitrophenyl alkanoates (C2 to C6) studied here. For these esters the kinetic parameters (Table II, A) do not vary markedly with the alkyl chain length, although for C3 to C6 there are upward trends in k_c/k_u and k_2 with α-CD and a downward trend in the values of K_{TS} for both CDs. These trends are much more evident if we include values for the C8 and C12 esters, studied earlier.[10] For example, the accelerations (k_c/k_u) for the C12 ester are appreciably higher: 11 (α-CD) and 67 (β-CD). Moreover, for the C5, C6, C8, and C12 esters the values of K_{TS} decrease by about a factor of 50 for both α- and β-CD. These significant dependences of K_{TS} on the acyl chain length of the esters **4** are consistent with there having been a switch from aryl to alkyl group binding in the transition state for cleavage by CDs (i.e., from **1** to **2**).

To emphasize this last point, we have plotted pK_{TS} (= $-\log K_{TS}$) vs the number of carbons in the alkyl chain length (N) for cleavage of the esters **3** and **4** with α-CD. As seen in Figure 2, there is a very good correlation for the *p*-nitrophenyl esters (C3 to C12; N = 2, 3, 4, 5, 7, 11)[24] with a significant slope, indicating a strong dependence on the length of the chain:

$$\alpha\text{-CD}/p\text{-nitro:}\quad pK_{TS} = 0.246(\pm 0.007)N + 1.80;\quad r = 0.998 \qquad (10a)$$

$$\alpha\text{-CD}/m\text{-nitro:}\quad pK_{TS} = 0.038(\pm 0.027)N + 4.16;\quad r = 0.703 \qquad (10b)$$

(24) The acetate is excluded because it is believed to react by aryl group inclusion. Also, as mentioned earlier, it may be different for steric reasons.

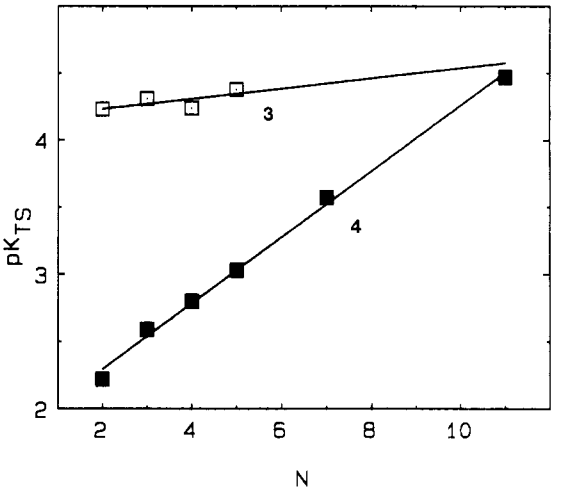

Figure 2. Chain length dependence of pK_{TS} (= $-\log K_{TS}$) for *m*- and *p*-nitrophenyl alkanoates **3** and **4**, respectively, reacting with α-cyclodextrin. The definition of K_{TS} is in eq 4. The horizontal axis is the number of carbons (N) in the alkyl portion of the acyl group of the ester. The correlation lines are defined by eqs 10a and 10b. Such plots are, in essence, linear free energy relationships (see text).

In contrast, for the *m*-nitrophenyl esters (C3 to C6, N = 2–5)[24] there is a poorer correlation with a slope close to 0 (eq 10b), indicating essentially no sensitivity to the length of the acyl chain. This striking difference, which is shown clearly by the two graphs in Figure 2, is strong evidence that the two series of esters react via different pathways. In particular, it is clear that the *p*-nitrophenyl esters **4** (C3 to C12) react via alkyl chain inclusion, while the *m*-nitro isomers **3** do not; they react via aryl group binding (Scheme I) because this pathway is so much better for them.

The lines described by eqs 10a and 10b intersect near N = 11 (Figure 1). Thus, if the extrapolation of eq 10b for *m*-nitro esters is valid, both of the C12 esters should

Table III. Constants for the Cleavage of 2-Carboxychlorophenyl Esters 5 and 6 in the Presence of Cyclodextrins[a]

acyl	K_S, mM	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u	k_2, M^{-1} s^{-1}	K_{TS}, mM
			(A) α-Cyclodextrin			
5-chloro						
C2	5.3	0.011	3.2	290	600	0.018
C3	7.6	0.0069	0.58	84	76	0.091
C4	7.4	0.0038	0.24	63	32	0.12
C5	4.5	0.0035	0.15	43	33	0.11
C6	11	0.0029	0.29	100	26	0.11
4-chloro						
C2	13	0.0071	0.022	3.1	1.7	4.2
C3	5.6	0.0062	0.011	1.8	2.0	3.1
C4	7.1	0.0038	0.0064	1.7	0.90	4.2
C5	8.6	0.0040	0.0092	2.3	1.1	3.7
C6	12	0.0028	0.016	5.7	1.3	2.2
			(B) β-Cyclodextrin			
5-chloro						
C2	16	0.011	0.58	53	36	0.31
C3	16	0.0069	0.13	19	8.1	0.85
C4	15	0.0036	0.057	16	3.8	0.95
C5	11	0.0035	0.038	11	3.5	1.0
C6	7.5	0.0029	0.024	8.3	3.2	0.91
4-chloro						
C2	22	0.0072	0.11	15	5.0	1.4
C3	12	0.0058	0.024	4.1	2.0	2.9
C4	11	0.0031	0.010	3.2	0.91	3.4
C5	6.9	0.0036	0.0079	2.2	1.1	3.3
C6	6.3	0.0026	0.0045	1.7	0.71	3.7

[a] At 25 °C, in 0.2 M phosphate buffer (pH 11.9).

react via alkyl group inclusion (see **2**) and the "meta/para" distinction would disappear, as envisaged at the outset.[25]

For esterolysis of *p*-nitrophenyl esters (C3 to C12; N = 2, 3, 4, 5, 7, 11) by β-CD there is a strong dependence on chain length, although the correlation of pK_{TS} with N is poorer (eq 11a), probably because of the different origins of the data: C3–C6 (this work), C8, and C12[10] (see Experimental Section for details).[26] Again, there is only a

$$\beta\text{-CD}/p\text{-nitro:}\quad pK_{TS} = 0.213(\pm 0.022)N + 2.47;\quad r = 0.978 \qquad (11a)$$

$$\beta\text{-CD}/m\text{-nitro:}\quad pK_{TS} = 0.079(\pm 0.023)N + 3.74;\quad r = 0.927 \qquad (11b)$$

weak dependence on N for the *m*-nitrophenyl esters (C3–C6, N = 2–5), with a slope close to 0 (eq 11b). Thus, as with α-CD, the two series of esters (**3** and **4**) appear to react via transition states with different modes of binding.

As discussed earlier, we also expect to find correlations of pK_S with N for the substrates, *if* alkyl group binding is dominant. Such is the case for the two series of esters **3** and **4**, as shown in Table I. This change in the mode of substrate binding[10] is consistent with the hydrophobicity (and size) of the alkyl chains of the esters. The Hansch hydrophobicity parameters (π)[17] for aromatic ester groups increase monotonically with their lengths (MeCOO, –0.64; EtCOO, –0.10; PrCOO, 0.44; BuCOO, 0.98; etc.), whereas π = –0.28 for the nitro group.[17c] Thus, while *p*-nitrophenyl acetate binds with its nitro group deep inside the CD cavity,[10] the longer esters bind in the inverse manner, with the ester group inside.

Obviously in cases where the values of pK_S and pK_{TS} are both linear in N, these constants correlate with one another in the form of LFERs. Furthermore, such correlations suggest similar modes of binding for the substrates and their transition states for ester cleavage, if their slopes are near 1. In the present work this behavior is seen for the *p*-nitrophenyl esters **4**, but not for their isomers **3**.

We now consider the possible significances of the slopes of the various correlation lines, presented above. For the esters **3** and **4** the correlations of pK_S (and pK_{TS} for **4**) with N have slopes ~0.2. The other substrates in Table I have higher slopes: alkanols (0.6), alkylphenols (0.6), alkylphenyl acetates (0.5, 0.4), and alkanesulfonate ions (0.3, 0.4). Thus, the slopes vary with the head group, and their values correspond to Gibbs energy increments of 0.3 to 0.8 kcal/mol per CH_2 group. For comparison, the Gibbs energies of transfer of aliphatic molecules from water to organic media have increments of 0.6 to 0.9 kcal/mol per CH_2 group, depending on the hydrophilic end group and the organic medium.[16]

Taken as a whole, our results and those of Bonora et al.[10] are consistent with three distinct conclusions: (1) the nitrophenyl alkanoates **3** and **4** bind to α- and β-CD through their alkyl chains; (2) *m*-nitrophenyl alkanoates **3** (to at least the hexanoate) undergo ester cleavage by both CDs through transition states involving aryl group binding (**1**); (3) the *p*-nitrophenyl alkanoates **4** beyond the acetate undergo ester cleavage through a transition state in which the alkyl chain is included in the CD cavity (**2**).[27]

2-Carboxychlorophenyl Esters. The constants for these substrates (**5** and **6**, C2–C6) are presented in Table III. Unlike some of the data in Table II, the parameters show no systematic variations with chain length. Values for the acetate are somewhat different, but this is probably due to steric factors, as mentioned above.

The values of K_s for substrate binding show little or no variation, and certainly no systematic decrease, with chain length. Thus, it appears that the chlorophenyl esters **5** and **6** bind through their aryl groups and not via their alkyl

(25) Unfortunately, practical considerations (low solubility of long chain esters[23] and the low extinction coefficient for *m*-nitrophenoxide ion) make it impossible to test this point.

(26) Also, the parameters for the C12 ester[10] may be less reliable because of the problems of aggregation.[23] Regardless of the poorer quality of the correlation (eq 11a), the difference between the behaviors of the *p*- and *m*-nitrophenyl esters is quite evident.

(27) We have recently obtained evidence that in the transition state for the cleavage of *p*-nitrophenyl acetate by β-CD the aryl group is *outside* the CD cavity. In brief, cleavage of *m*-nitrophenyl acetate is subject to competitive inhibition by various species, whereas that of the *p*-nitro isomer is not: Tee, O. S.; Hoeven, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8318.

chains. Apparently, the chlorophenyl moieties are of sufficient size and hydrophobicity to compete with the alkyl chains for binding to the CDs. This is not as unreasonable as it might seem, since the partition coefficient (H_2O–octanol) for *p*-chlorophenol (log P = 2.4) is greater than that for hexanol (2.0) or hexanoic acid (1.9).[17c]

There are also no clear trends in the kinetic parameters associated with reaction of the esters **5** and **6**. Throughout, the 5-chloro esters **5** are cleaved more easily by both α- and β-CD, regardless of the chain length. With α-CD the 5-chloro esters are consistently 20–30 times more reactive than their 4-chloro isomers, except for the acetate, which is 350 times more reactive. Similar behavior is seen with β-CD, although the differences between the two series of esters (**5** and **6**) are smaller. Beyond the acetate, the values of K_{TS}, k_c/k_u, and k_2 are all remarkably constant within each series (C3 to C6) and for each CD (Table III). It seems, therefore, that with these esters aryl group inclusion is dominant for both the substrate *and* for the transition state for cleavage, unlike the *p*-nitrophenyl esters, discussed above.

The difference in behavior between the nitrophenyl esters (**3** and **4**) and the chlorophenyl esters (**5** and **6**) is ascribed to the greater hydrophobicity of the chlorophenyl substituent, since the value of π for aryl Cl (0.71) is appreciably greater than that for aryl NO_2 (−0.28).[17c] Also, the binding of the chlorophenyl groups may be assisted by the *o*-carboxyl functionality, which can accept hydrogen bonds from solvent molecules and the secondary hydroxyl groups at the lip of the CD cavity.[6]

Conclusions

The cleavage of *p*-nitrophenyl alkanoates by α- and β-cyclodextrins in basic solution is quite sensitive to the length of the acyl chains, whereas that of the isomeric *m*-nitrophenyl esters is much less so, at least to C6. It appears that the *p*-nitrophenyl esters (beyond the acetate) undergo esterolysis through a transition state in which the alkyl chain is included in the cavity of the cyclodextrin. In contrast, the *m*-nitrophenyl esters react through aryl inclusion, since this mode is much more efficient for a meta substituent. For both series of esters (beyond the acetate) substrate binding is through alkyl chain inclusion. Thus, as shown in other studies,[13,27] the modes of substrate binding and transition-state binding are not necessarily the same.

In contrast to the foregoing, the cleavage of the 2-carboxychlorophenyl esters **5** and **6** show virtually no dependence on the length of the acyl chain. Apparently, these esters bind to CDs by aryl group inclusion in both the initial state *and* the transition state for esterolysis.

As discussed in detail elsewhere,[13] the apparent dissociation constants K_{TS} are useful parameters for the probing the structure of transition states of reactions mediated by cyclodextrins. Also, linear free energy relationships based on values of pK_S (= −log K_S) and pK_{TS} (= −log K_{TS}) can be used to make distinctions between the modes of binding of substrates and transition states.

Experimental Section

The *p*-nitrophenyl esters were obtained from the Sigma Chemical Company and organic starting materials from Aldrich Chemical Company. The *m*-nitrophenyl esters were synthesized from *m*-nitrophenol and the appropriate acid anhydride, with catalysis by sulfuric acid.[28] The 2-carboxyphenyl esters **5** and **6** were prepared likewise from the appropriate salicylic acid. The highly discolored 4-chlorosalicylic acid was dissolved in EtOH, decolorized with charcoal, and recrystallized from EtOH–water several times before use. All of the esters gave appropriate ^1H NMR spectra and the requisite increase in absorbance due to the phenolate upon hydrolysis in basic solution.

Kinetic measurements were carried out in *strong* phosphate buffers (0.2 M) because the pHs employed (11.7 or 11.9) are close to the pK_as of the secondary hydroxyl groups of α- and β-CD (12.2, 12.3).[29] Using weaker buffers, or dilute NaOH solutions, one observes distorted saturation curves that can easily be misinterpreted as indicating 2:1 (CD:substrate) binding. The distortions arise because added CD exerts a buffering action that lowers the pH of the medium.

Ester solutions were made by dilutions of stock solutions in HPLC grade methanol. As a result, the final reacting solutions contained 0.1% (v/v) MeOH. Ester concentrations were $[3]_0$ = 0.1–0.5 mM; $[4]_0$ = 0.01–0.05 mM; $[5 \text{ or } 6]_0$ = 0.5 mM. For the chloro esters **5** and **6** slightly less than 1 equiv of NaOH was added to the substrate solutions to ionize their carboxyl groups and so facilitate solubilization. Experiments with longer esters (C8, C10, and C12) were not successful, under the reaction conditions employed. With such esters solubility in aqueous media is problematical, and even when they appear to have dissolved completely the kinetics of esterolysis may be complicated due to partial aggregation.[23] This problem of solubility is particularly acute for **3** because one must employ higher ester concentrations to compensate for the lower extinction coefficient of *m*-nitrophenoxide ion.

The cleavage reactions were monitored at the appearance of the phenolate anions, as follows: *p*-nitrophenoxide ion at 405 nm; *m*-nitrophenoxide, 390 nm; 4-chloro and 5-chlorosalicylate, 310 nm. Although some of the reactions are not particularly fast, rates were measured on an Aminco-Morrow stopped-flow apparatus on an Aminco DW2 UV–vis spectrophotometer, interfaced to an Apple II microcomputer.[6] The observation cell was maintained at 25.0 ± 0.1 °C. Absorbance values were collected over 10 half-lives, and those covering about 90% reaction were analyzed to yield pseudo-first-order rate constants, k^{obsd}.[6]

Values of k^{obsd} were normally obtained at [CD] = 0 (=k_u), 1, 2, 4, 6, 8, 10 mM. All of the substrates, except one (see below), gave saturation-type kinetics and good analyses by the Eadie–Hofstee approach,[1] Lineweaver–Burk approach,[1] and by nonlinear least-squares fitting to eq 3.[30] Concentration series that did not give good agreement between the three different methods were repeated. The results of the Eadie–Hofstee analyses (Tables S1–S4) were used to provide the constants k_c and K_S, given in Tables II and III, since they are considered to be more reliable than those obtained from the Lineweaver–Burk method of analysis.[31]

Simple saturation behavior was not observed for *p*-nitrophenyl propanoate reacting with α-CD. In several trials these reactants consistently gave values of k^{obsd} that were not reproduced well by eq 3. The data gave strongly curved Eadie–Hofstee and Lineweaver–Burk plots and poor nonlinear fits of eq 3 (see Figure 3a). The added curvature may be explained by the presence of a nonproductive 2:1 (CD:substrate) binding, which causes the data to level off more acutely at high [CD]. We have observed similar behavior with other aryl esters.[12]

The presence of the additional equilibrium S·CD + CD ⇌ S·CD_2 requires that eq 3 be expanded to

$$k^{obsd} = \frac{(k_u K_s + k_c[CD])K_2}{(K_s K_2 + K_2[CD] + [CD]^2)} \qquad (12)$$

where K_2 is the dissociation constant for the second equilibrium. As seen in Figure 3, this equation gives a much better fit to the data than does eq 3, with the constants K_S = 11.6 ± 3.1 mM, K_2 = 37.2 ± 14.9 mM, k_c = 0.203 ± 0.023 s^{-1} (r = 0.9996, χ^2 = 6.27 × 10^{-7}); fitting of eq 3 gave K_S = 4.32 ± 0.56 mM, k_c = 0.146 ±

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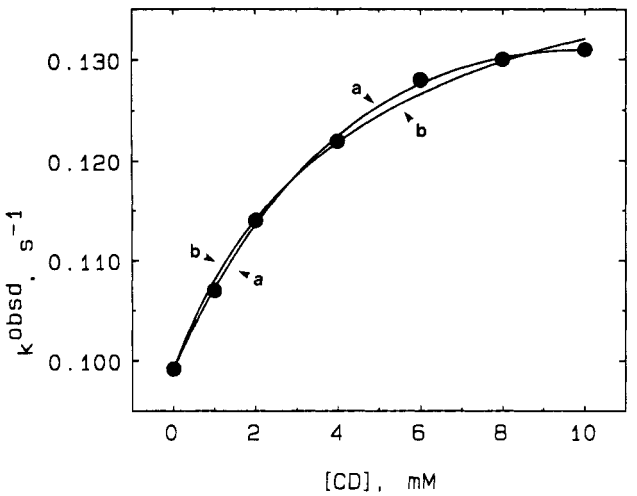

Figure 3. Data for the cleavage of *p*-nitrophenyl propanoate by α-CD. Curve (a) for the model including nonproductive 2:1 binding (eq 12) is clearly superior to that (b) for productive 1:1 binding alone (eq 3). See discussion in the Experimental Section.

0.003 s^{-1} (r = 0.9976, $\chi^2 = 4.39 \times 10^{-6}$).

For the *p*-nitrophenyl esters C2, C4, and C6 there is reasonable agreement with the values of K_S and k_c/k_u obtained earlier,[10] given the differences in reaction conditions (pH 10.4, 1% (v/v) MeCN), the range of [CD] employed (0–5 mM), and the method of analysis (Lineweaver–Burk). The agreement is very good for α-CD but only fair with β-CD. Nevertheless, the discrepancies for β-CD are not large enough to affect any of our conclusions. Our values of k_c/k_u and K_S for the acetates agree well with those of earlier workers.[3,6,7,10]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for an operating grant to O.S.T. and Mr. Bryan Takasaki for initial technical assistance. Professor K. Murakami (Kyushu University) kindly provided a copy of ref 20.

Registry No. **3** (R = Me), 1523-06-4; **3** (R = Me)/α-CD complex, 120040-15-5; **3** (R = Me)/β-CD complex, 74091-81-9; **3** (R = Et), 69844-29-7; **3** (R = Et)/α-CD complex, 126375-48-2; **2** (R = Et)/β-CD complex, 126375-56-2; **3** (R = Pr), 14617-97-1; **3** (R = Pr)/α-CD complex, 126375-49-3; **3** (R = Pr)/β-CD complex, 126375-57-3; **3** (R = Bu), 126375-39-1; **3** (R = Bu)/α-CD complex, 126375-50-6; **3** (R = Bu)/β-CD comp, 126375-58-4; **3** (R = $(CH_2)_4CH_2$), 126375-40-4; **3** (R = (CH_2CH_3)/α-CD complex, 126375-51-7; **3** (R = $(CH_2)_4CH_3$)/β-CD complex, 126421-20-3; **4** (R = Me), 830-03-5; **4** (R = Me)/α-CD complex, 120040-16-6; **4** (R = Me)/β-CD complex, 74069-32-2; **4** (R = Et), 1956-06-5; **4** (R = Et)/α-CD 1:1 complex, 126375-52-8; **4** (R = Et)/α-CD 1:2 complex, 126375-55-1; **4** (R = Et)/β-CD complex, 126421-21-4; **4** (R = Pr), 2635-84-9; **4** (R = Pr)/α-CD complex, 126375-53-9; **4** (R = Pr)/β-CD complex, 126375-59-5; **4** (R = Bu), 1956-07-6; **4** (R = Bu)/α-CD complex, 126375-54-0; **4** (R = Bu)/β-CD complex, 126421-22-5; **4** (R = $(CH_2)_4CH_3$)/α-CD complex, 126421-19-0; **4** (R = $(CH_2)_4CH_3$)/β-CD complex, 126421-23-6; **5** (R = Me), 17336-08-2; **5** (R = Me)/α-CD complex, 126375-60-8; **5** (R = Me)/β-CD complex, 126375-70-0; **5** (R = Et), 126375-41-5; **5** (R = Et)/α-CD complex, 126375-61-9; **5** (R = Et)/β-CD complex, 126375-71-1; **5** (R = Pr), 126375-42-6; **5** (R = Pr)/α-CD complex, 126375-62-0; **5** (R = Pr)/β-CD complex, 126375-72-2; **5** (R = Bu), 126375-43-7; **5** (R = Bu)/α-CD complex, 126375-63-1; **5** (R = Bu)/β-CD complex, 126421-24-7; **5** (R = $(CH_2)_4(CH_3)$, 126375-44-8; **5** (R = $(CH_2)_4CH_3$)/α-CD, 126375-64-2; **5** (R = $(CH_2)_4CH_3$)/β-CD, 126375-73-3; **6** (R = Me), 1734-62-9; **6** (R = Me)/α-CD complex, 126375-65-3; **6** (R = Me)/β-CD complex, 126375-74-4; **6** (R = Et), 1760-88-9; **6** (R = Et)/α-CD complex, 126375-66-4; **6** (R = Et)/β-CD complex, 126375-75-5; **6** (R = Pr), 126375-45-9; **6** (R = Pr)/α-CD complex, 126375-67-5; **6** (R = Pr)/β-CD complex, 126375-76-6; **6** (R = Bu), 126375-46-0; **6** (R = Bu)/α-CD complex, 126375-68-6; **6** (R = Bu)/β-CD complex, 126375-77-7; **6** (R = $(CH_2)_4CH_3$), 126375-47-1; **6** (R = $(CH_2)_4CH_3$)/α-CD complex, 126375-69-7; **6** (R = $(CH_2)_4CH_3$)/β-CD complex, 126375-78-8; α-CD, 10016-20-3; β-CD, 7585-39-9; *m*-nitrophenol, 554-84-7; 4-chlorosalicylic acid, 5106-98-9; 5-chlorosalicylic acid, 321-14-2; acetic anhydride, 108-24-7; propionic anhydride, 123-62-6; butyric anhydride, 106-31-0; pentanoic anhydride, 2082-59-9; hexanoic anhydride, 2051-49-2.

Supplementary Material Available: Tables of first-order rate constants for the cleavage of the esters **3**, **4**, **5**, and **6** as a function of the [α-CD] and [β-CD] (Tables S1–S4) (5 pages). Ordering information is given on any current masthead page.

The β-Effect: Changing the Ligands on Silicon[1]

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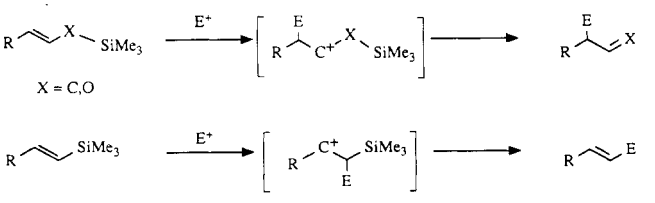
Received December 27, 1989

The ability of a silyl group to stabilize a carbocation β to silicon, the β-effect, is directly related to the electron-withdrawing ability of the groups on silicon. This was shown by using the degree of syn addition of bromine to (*E*)-β-silylstyrenes as a measure of the stabilizing ability. With the exception of alkoxysilanes and phenoxysilanes, a good correlation between the degree of the β-effect and the group electronegativity of the silyl group is observed. The special case of the alkoxysilanes and phenoxysilanes is discussed in the context of the addition mechanism.

The remarkable interest in the use of silicon in organic synthesis and, increasingly, in other fields of chemistry stems from the "unusual" properties[3] that this element conveys to organic molecules. Arguably, the most important of these properties is the β-effect, the ability of silicon to stabilize a carbocation in the β-position. The β-effect has been invoked mechanistically in most of the reactions that involve silicon–carbon bond cleavage (and, usually, carbon–carbon bond formation) under acidic conditions. Such reactions include the Lewis acid cata-

Scheme I



(1) A preliminary account of the work has appeared: Brook, M. A.; Neuy, A.; Hadi, M. A. *J. Chem. Soc., Chem. Commun.* **1989**, 957.
(2) NSERC University Research Fellow, 1985–1990.
(3) The properties are unusual only when carbon-based chemistry is used as a standard against which to measure group IV chemical reactivity.

0022-3263/90/1955-3609$02.50/0