δ 37.59, 38.03, 41.55, 58.45, 126.29, 128.38, 128.70, 138.33; EIMS, *m/z* 157 (62), 129 (100), 128 (36), 117 (59), 116 (55), 115 (94), 91 (93), 65 (40), 39 (35); HRMS, *m/z* (calcd for $C_{12}H_{13}$: 157.1017) 157.1022. Minor products were identified by GCMS as bibenzyl and remaining [2]**1u**. Attempts at purification of 1-benzyl-3-bromobicyclo[1.1.1]pentane by low temperature recrystallization were unsuccessful.

1-Bromo-3-*tert*-butylbicyclo[1.1.1]pentane ([1]1v). A solution of **1** prepared from 50 mmol of **8** in pentane, *tert*-butyl bromide (35 mL), and benzoyl peroxide (0.1 g) is irradiated in a round-bottomed flask for 10 h. Evaporation of the solvent and excess *tert*-butyl bromide followed by short-path vacuum distillation gives 3.1 g of a semicrystalline fraction. Low-temperature crystallization from pentane gives 1.67 g (16% yield based on **8**) of white crystals: mp 80.5-81.0 °C; ^{1}H NMR δ 0.84 (s, 9 H), 2.03 (s, 6 H); ^{13}C NMR δ 26.45, 31.02, 37.62, 49.65, 55.48; IR 2963, 1199, 1148, 850 cm^{-1}; EIMS *m/z* 205 (2), 123 (12), 107 (28), 91 (62); HRMS *m/z* (calcd for C_9H_{15} 123.1174) 123.1178. Anal. Calcd for $C_9H_{15}Br$: C, 53.21; H, 7.44; Br, 39.34. Found: C, 53.15; H, 7.44; Br, 39.25.

Preparative GC isolation of higher oligomers from a fraction of the residue (1.25 g) from the distillation was attempted. Crude [2]**1v** was recrystallized from pentane at -78 °C: ^{1}H NMR δ 0.80 (s, 9 H), 1.41 (s, 6 H), 2.07 (s, 6 H); ^{13}C NMR δ 25.85, 29.38, 35.52, 37.63, 41.63, 46.03, 47.23, 57.22; IR 2962, 2869, 1361, 1135, 835 cm^{-1}.

Preparation of 27 and 28 by Reaction of Tetraethyl Hypophosphite with 1. An ethereal solution of tetraethyl hypophosphite[85] (6.4 g, 26 mmol) and **1**, prepared from 35 mmol of **8**, is irradiated for 8 h. When no further reaction is observed by GC monitoring, the flask containing the adducts is opened to the air and stirred at room temperature overnight. The resulting viscous yellow oil is passed through a silica gel column (200 g). Elution with ethyl acetate gives 2.0 g of low molecular weight side products not containing the bicyclo[1.1.1]pentane moiety, as determined by NMR and GCMS. Change of the eluent to acetone/ethyl acetate (7:3) permits the collection of a wide band of yellowish product (2.0 g), which after short-path distillation (170 °C/0.1 mmHg) gives 1.64 g (19% yield based on **8**) of 1,3-bis(diethoxyphosphoryl)bicyclo[1.1.1]-pentane (**27**) as a colorless oil: ^{1}H NMR δ 1.22 (td, J_1 = 7.1 Hz, J_2 = 1.1 Hz, 12 H), 2.21-2.22 (m, 6 H), 3.95-4.05 (m, 8 H); ^{13}C NMR δ 16.31 (d, J = 2.3 Hz), 36.52 (A_2X), 51.54, 61.73 (t, J = 3.0 Hz); ^{31}P NMR (H_3PO_4) δ 15.9; IR (neat) 1244, 1220, 1050, 1027, 968 cm^{-1}; EIMS, *m/z* 340 (2), 339 (2), 203 (100), 175 (38), 147 (72); CIMS (CH_4), *m/z* 342 (13), 341 (100); CI HRMS, *m/z* (calcd for $C_{13}H_{26}O_6P_2$ 341.1283) 341.1283. Anal. Calcd for $C_{13}H_{26}O_6P_2$: C, 45.88; H, 7.70; P, 18.20. Found: C, 45.93; H, 7.89; P, 18.02.

Further elution with methanol gave an oily yellow fraction which after drying in vacuum (200 °C/0.1 mmHg) yielded 3.80 g of crude ethyl *P,P*-bis(3-diethoxyphosphorylbicyclo[1.1.1]pent-1-yl)phosphinate (**28**). This byproduct was not purified further: ^{1}H NMR (major peaks) δ 1.20-1.30 (m, 15 H), 2.20-2.22 (m, 12 H), 3.91-4.05 (m, 10 H); ^{13}C NMR (major peaks) δ 16.23 (d, J = 3.3 Hz, 4C), 16.53 (d, J = 4.1 Hz), 37.43 (dd, J_1 = 155.8 Hz, J_2 = 30.0 Hz), 38.09 (dd, J_1 = 91.7 Hz, J_2 = 32.3 Hz), 51.81 (3C), 60.63 (d, J_1 = 6.3 Hz), 61.84 (d, J = 6.7 Hz, 4C); EIMS, *m/z* 497 (2), 405 (9), 361 (32), 295 (100), 211 (46), 203 (76), 175 (40), 173 (71), 147 (96), 143 (58), 129 (34), 65 (41); CIMS, *m/z* 500 (8), 499 (40), 339 (25), 311 (100); CI HRMS, *m/z* (calcd for $C_{20}H_{38}O_8P_3$ 499.1780) 499.1772.

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Multiple Behaviors in the Cleavage of Aryl Alkanoates by α- and β-Cyclodextrins. Processes Involving Two Molecules of Cyclodextrin

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Abstract: The kinetics of ester cleavage of 4-carboxy-2-nitrophenyl alkanoates (**1**) (C2-C8) and of 2-carboxy-4-nitrophenyl alkanoates (**2**) (C2, C4, C6, C8) in an aqueous phosphate buffer (pH 11.7) containing α- or β-cyclodextrin (α- or β-CD) show various types of behavior. Depending on the ester, its acyl chain, and the CD, the kinetics show acceleration (with or without saturation), retardation, acceleration and retardation, retardation and acceleration, or two kinds of acceleration. However, this diversity can be rationalized with simple reaction schemes. Short-chain esters mainly react conventionally through binary CD-ester complexes. For longer chains, some ester/CD combinations exhibit nonproductive 2:1 (CD:ester) binding, whereas other combinations show a cleavage process involving two CD molecules. The latter is most likely due to the attack of a CD (anion) on the 1:1 CD-ester complex *or* to reaction within a weak 2:1 complex. Modes of transition-state binding are probed using the pseudoequilibrium constants (K_{TS}) introduced in earlier work (*Carbohydr. Res.* **1989**, *192*, 181).

Introduction

The cleavage of aryl esters in the presence of cyclodextrins[1] (CDs) in basic aqueous solution has been studied extensively.[1-12] Various types of esters have been employed, and the dependencies of the rate accelerations (or retardations) on structure have been

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Table I. Constants for the Cleavage of 4-Carboxy-2-nitrophenyl Alkanoates (**1**) in the Presence of α-Cyclodextrin[a]

acyl	K_1, mM	K_2, mM	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u	k_2, M^{-1} s^{-1}	K_{TS}, mM
C2	9.6 ± 0.4		0.096	0.174 ± 0.002	1.8	18	5.3
C3	17 ± 4	8.8 ± 0.9	0.050	0.061 ± 0.002	1.2	3.6	14
C4	7.7 ± 1.1	14 ± 2	0.027	0.013 ± 0.002	0.48	1.7	16
C5	2.1 ± 0.9	22 ± 3	0.029	0.022 ± 0.002	0.76	10	2.8
C6	1.4 ± 0.2	29 ± 1	0.027	0.038 ± 0.001	1.4	27	1.0
C7	1.1 ± 0.1	17 ± 1	0.026	0.063 ± 0.002	2.4	57	0.46
C8	0.50 ± 0.06	26 ± 2	0.022	0.074 ± 0.002	3.4	150	0.15
2EtC6	2.3 ± 0.2		0.0010	(1.88 ± 0.02) × 10^{-3}	1.9	0.83	1.2
4MeC5	1.2 ± 0.2		0.025	0.0172 ± 0.0004	0.69	14	1.7

[a] At 25 °C and in an aqueous phosphate buffer of pH 11.7. The cited uncertainties are the standard deviations obtained from the nonlinear fitting procedure.

examined. However, there have been few studies in which the acyl groups of simple alkanoates were varied systematically in such a way that the effects of inclusion of the alkyl chain in the cyclodextrin cavity could be probed.

Bender and co-workers[2a] found that the cleavage of 4-carboxyphenyl acetate is accelerated by α-CD,[13] but cleavage of the analogous 2-methylpropanoate and 3,3-dimethylbutanoate is retarded. This retardation is due to stronger binding of the alkyl chain in the substrate–CD complexes than in the corresponding transition states.[2a,9] More recently, Italian workers[10] studied the esterolytic behavior of *p*-nitrophenyl alkanoates (C2, C4, C6, C8, C12) in the presence of α- and β-CD.[13] In all cases, the rate of cleavage is modestly enhanced, and the variation of the kinetic parameters with acyl chain length is consistent with a change of the mode of binding of the ester from aryl to alkyl group inclusion.[9-11] Related studies, carried out in our laboratory, confirmed these findings for *p*-nitrophenyl esters (C2–C6) and also showed that, in contrast, *m*-nitrophenyl alkanoates (C2–C6) undergo cleavage from ester–CD complexes in which the aryl group is bound in the CD cavity.[11]

In the present paper, we report that the ease of cleavage of 4-carboxy-2-nitrophenyl alkanoates by cyclodextrins varies substantially with the length of the acyl chain (C2–C8). For the longer esters there are processes which involve *two* molecules of the CD, but these processes are different for α- and β-CD: one is inhibitory, the other is not. Some 2-carboxy-4-nitrophenyl esters show cleavage with two molecules of CD for *both* α- and β-CD. A preliminary communication has appeared.[12]

Results

We have measured the rates of esterolysis of nine 4-carboxy-2-nitrophenyl alkanoates (**1**) in an aqueous phosphate buffer (pH 11.7) as a function of the concentration of α- or β-CD (Tables S1 and S2, supplementary material). Four 2-carboxy-4-nitrophenyl esters (**2**) were also studied (Table S3). The esters **1** and **2** were chosen because in basic solution, where their carboxyl groups are ionized, they should be reasonably water-soluble. Also, their aryl groups should be more hydrophilic than the nitrophenyl groups of the esters studied earlier,[10,11] so that a decided preference for binding of their acyl chains to CDs should be present. Thus, the esters **1** and **2** appeared to have potential as probes of the binding of alkyl chains in CD cavities[14] and of the effects of such binding on reactivity.

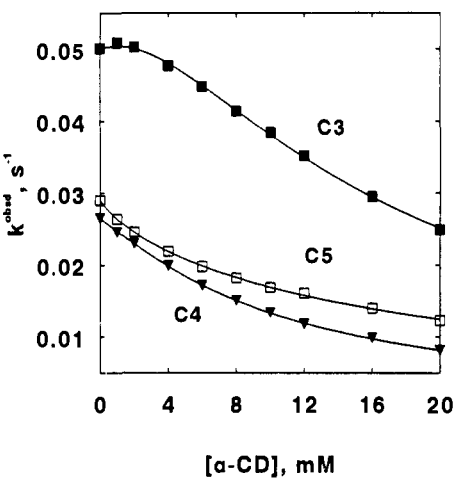
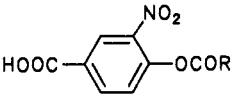
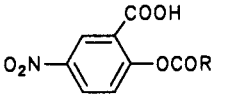


Figure 1. Plots of k^{obsd} vs [α-CD] for the cleavage of 4-carboxy-2-nitrophenyl (**1**) propanoate (C3), butanoate (C4), and pentanoate (C5) esters. The curves were generated from eq 4 with the fitted constants in Table I.



1: acetate (C2)
propanoate (C3)
butanoate (C4)
pentanoate (C5)
hexanoate (C6)
heptanoate (C7)
octanoate (C8)
2-ethylhexanoate (2EtC6)
4-methylpentanoate (4MeC5)



2: acetate (C2)
butanoate (C4)
hexanoate (C6)
octanoate (C8)

The results greatly exceeded our expectations in that unusual behaviors were revealed.[12] Depending on the ester (**1** or **2**), its alkyl chain length, and the CD (α or β), the esters show varying

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

(14) As discussed elsewhere[9,11] and later in the present paper, the binding of alkyl chains is well-documented. For example, CDs form inclusion complexes with linear alcohols, alkylphenols, acylphenols,[8] and alkanesulfonate ions (and other surfactants).[15]

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Table II. Constants for the Cleavage of 4-Carboxy-2-nitrophenyl Alkanoates (**1**) in the Presence of β-Cyclodextrin[a]

acyl	K_1, mM	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u	k_{c2}, M^{-1} s^{-1}	k_2, M^{-1} s^{-1}	K_{TS}, mM
C2	6.5 ± 0.3	0.096	0.276 ± 0.004	2.9		42	2.2
C3	5.5 ± 0.2	0.050	0.033 ± 0.0002	0.66		6.0	8.3
C4	1.5 ± 0.02	0.029	0.0078 ± 0.0001	0.27		5.2	5.6
C5	0.76 ± 0.04	0.031	0.0042 ± 0.0003	0.14	*b*	5.5	5.4
C6	0.38 ± 0.03	0.024	0.0067 ± 0.0003	0.28	0.15 ± 0.03	18	1.4
C7	0.27 ± 0.01	0.026	0.0142 ± 0.0002	0.55	0.24 ± 0.02	52	0.49
C8	0.79 ± 0.10	0.022	0.0263 ± 0.0002	1.2	0.54 ± 0.02	33	0.66
2EtC6	0.45 ± 0.02	0.0010	(9.3 ± 0.8) × 10^{-5}	0.09	(8.5 ± 0.9) × 10^{-3}	0.21	4.8
4MeC5	0.26 ± 0.02	0.026	0.0048 ± 0.003	0.18	0.10 ± 0.03	18	1.4

[a] As in Table I. [b] Fitting eq 6 gives a value of k_{c2} with large uncertainty, and the correlation is only slightly better.

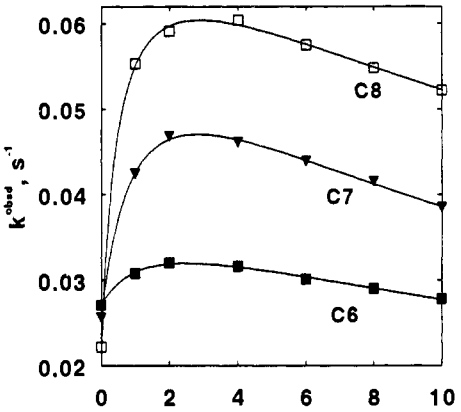

Figure 2. Plots of k^{obsd} vs [α-CD] for the cleavage of 4-carboxy-2-nitrophenyl (**1**) hexanoate (C6), heptanoate (C7), and octanoate (C8) esters. The calculated curves were generated from eq 4 with the fitted constants in Table I.

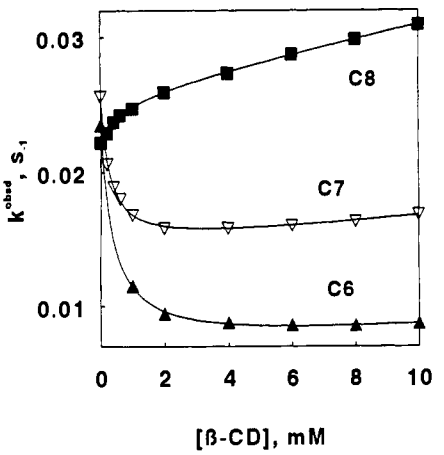

Figure 3. Plots of k^{obsd} vs [β-CD] for the cleavage of 4-carboxy-2-nitrophenyl (**1**) hexanoate (C6), heptanoate (C7), and octanoate (C8) esters. The calculated curves were generated from eq 6 with the fitted constants in Table II.

dependences of the rate of cleavage on [CD]: acceleration (with or without saturation), retardation, acceleration and retardation, retardation and acceleration, or two kinds of acceleration! Nevertheless, this diversity may be rationalized by simple reaction schemes.

Cleavage of the acetate of **1** in the presence of α-CD, like that of most esters,[1-11] exhibits simple, saturation kinetics[2a,b,7] which are consistent with reaction of the unbound substrate (S) and of a 1:1 substrate–CD complex:

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

$$S + CD \underset{K_1}{\rightleftharpoons} S\text{–}CD \xrightarrow{k_c} P \qquad (1b)$$

$$k^{obsd} = \frac{(k_u K_1 + k_c[CD])}{(K_1 + [CD])} \qquad (2)$$

The values of k^{obsd} increase modestly with [CD], since k_c/k_u = 1.6, and the ester binds moderately to α-CD (K_1 = 9.6 mM) (Table I).

Esterolysis of the C3, C4, and C5 esters of **1** is retarded by α-CD (Figure 1), whereas that of the C6, C7, and C8 esters is enhanced (Figure 2). However, none of these esters show simple saturation kinetics,[16] and with the three longest esters an additional, *inhibitory* process is evident at high [CD] (Figure 2). These results conform to the intrusion of nonproductive 2:1 binding (eq 3), in addition to the processes shown in eqs 1a,b.

$$S\text{–}CD + CD \underset{K_2}{\rightleftharpoons} S\text{–}CD_2 \qquad (3)$$

This additional equilibrium requires that eq 2 be replaced by

$$k^{obsd} = \frac{(k_u K_1 + k_c[CD])K_2}{(K_1K_2 + K_2[CD] + [CD]^2)} \qquad (4)$$

Equation 4 gives good fits to the data for the C3,[17] C4, C5 (Figure 1), C6, C7, and C8 esters (Figure 2), with the constants presented in Table I.

In contrast to the linear alkanoate esters just discussed, the branched esters (2EtC6 and 4MeC5) showed no evidence of 2:1 binding with α-CD; their behavior was adequately represented by eq 2, with the constants in Table I. With the 2-ethylhexanoate, increasing [CD] brings about a modest increase in rate ($k_c > k_u$), whereas with the 4-methylpentanoate there is a slight decrease.

Rate data for esterolysis of the C2, C3, C4, and C5 esters of **1** with β-CD (Table S2) all conform well to eq 2, that is, with the simple reaction of 1:1 ester–CD complexes (eq 1b). Cleavage of the acetate is accelerated (k_c/k_u = 2.9), but that of the next three esters is retarded ($k_c < k_u$) (Table II). For the longest esters (C6, C7, C8), however, different behavior is observed: cleavage of the C6 and C7 esters is retarded, but another process becomes significant at high [CD] (Figure 3). In the case of the C8 ester, there is no retardation and the additional process is dominant over most of the range of [CD] (Figure 3).

The rate data for the C6, C7, and C8 esters with β-CD may be rationalized by the processes in eqs 1a,b, together with a

(16) Deviations from normal behavior (eq 2) are most evident in curved Eadie–Hofstee plots, less so in Lineweaver–Burk plots.[1a,7]

(17) (a) Data for the C3 ester of **1** gave us considerable difficulties. The normal cleavage is retarded but, since the rate decrease is almost linear (Figure 1), the fitting of curvilinear equations was problematical. At best, such fitting yields constants with large uncertainties. More often than not, the nonlinear least-squares fitting procedure is "unstable" and the iterative calculation does not converge easily.[18] To try to overcome this problem we obtained rate data over a broader than normal range of [CD], in the hopes of maximizing the curvature in the data. In this way we were able to obtain rate data which gave a reasonable fit with eq 4, but never with eq 2. (b) If the point for the C3 ester at [α-CD] = 20 mM is omitted, the fit is no better (r = 0.9995) and the parameters are slightly different: K_1 = 11.8 ± 3.2 mM, K_2 = 10.4 ± 1.2 mM, k_c = 0.0604 ± 0.0014 s^{-1} (k_c/k_u = 1.2, K_{TS} = 9.8 mM).

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Table III. Constants for the Cleavage of 2-Carboxy-4-nitrophenyl Alkanoates (**2**) in the Presence of α- and β-Cyclodextrin[a]

acyl	K_1, mM	k_u, s^{-1}	k_c, s^{-1}	k_c/k_u	k_{c2}, M^{-1} s^{-1}	k_2, M^{-1} s^{-1}	K_{TS}, mM
			(a) α-Cyclodextrin				
C2	[b]	0.011	[b]	[b]		0.71 ± 0.01[c]	15[c]
C4	5.0 ± 0.9	0.0052	0.018 ± 0.002	3.5	0.38 ± 0.05	3.7	1.4
C6	4.7 ± 1.1	0.0054	0.018 ± 0.002	3.3	0.56 ± 0.10	3.8	1.4
C8	0.94 ± 0.15	0.0051	0.020 ± 0.001	3.9	0.47 ± 0.08	21	0.24
			(b) β-Cyclodextrin				
C2	27 ± 3	0.0100	0.093 ± 0.007	9.3		3.4	2.9
C4	8.8 ± 1.8	0.0053	0.0083 ± 0.0004	1.6		0.94	5.5
C6	1.9 ± 0.2	0.0053	0.0066 ± 0.0001	1.2	0.059 ± 0.006	3.5	1.6
C8	0.98 ± 0.05	0.0051	0.012 ± 0.0002	2.4	0.19 ± 0.01	12	0.41

[a] As in Table I. [b] Not available since saturation kinetics (eq 2) were not observed. [c] The value of k_2 is the slope of the linear plot of k^{obsd} vs [α-CD], and $K_{TS} = k_u/k_2$ (eq 8).

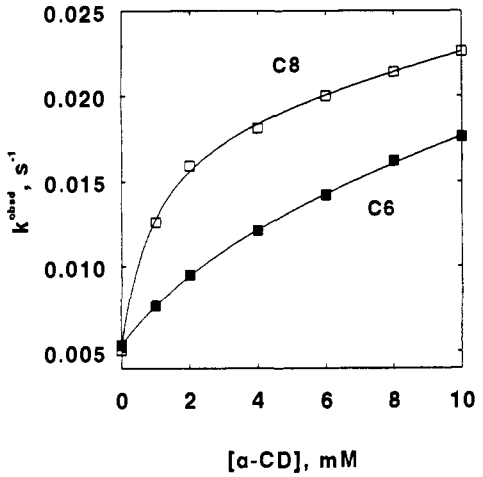


Figure 4. Plots of k^{obsd} vs [α-CD] for the cleavage of 4-carboxy-2-nitrophenyl (**2**) hexanoate (C6) and octanoate (C8) esters. The curves were generated from eq 6 with the fitted constants in Table III.

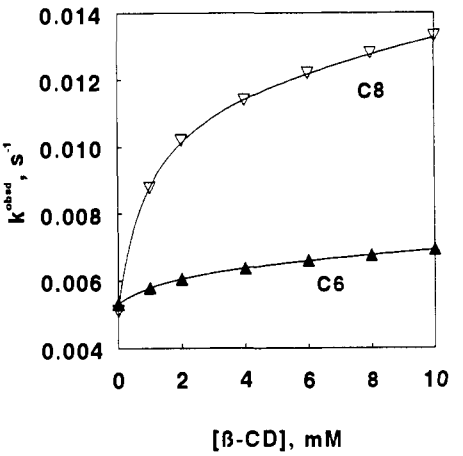


Figure 5. Plots of k^{obsd} vs [β-CD] for the cleavage of 4-carboxy-2-nitrophenyl (**2**) hexanoate (C6) and octanoate (C8) esters. The curves were generated from eq 6 with the fitted constants in Table III.

cleavage process involving a second molecule of CD, which is conceivably due to the attack of a CD on the ester–CD complex:

$$\text{S–CD} + \text{CD} \xrightarrow{k_{c2}} \text{P} \qquad (5)$$

$$k^{obsd} = \frac{(k_u K_1 + k_c[\text{CD}] + k_{c2}[\text{CD}]^2)}{(K_1 + [\text{CD}])} \qquad (6)$$

The presence of this second process means that eq 2 must be expanded to eq 6. This equation gives good-to-excellent fits to the data for the C6, C7, and C8 esters reacting with β-CD (Figure 3), and also for the two branched esters (**1**; 2EtC6, 4MeC5); the fitted constants are collected in Table II.

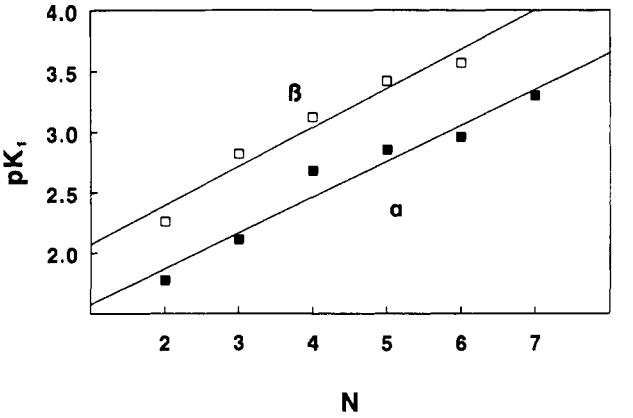


Figure 6. Dependence of pK_1 on N, the number of alkyl chain carbons, for the esters **1** binding to α- and β-CD. The lines are eqs 7a and 7b. For β-CD the C8 ester is omitted from the correlation.

Esterolysis of four 2-carboxy-4-nitrophenyl esters **2** with α- and β-CD was also studied (Table S3). In contrast to the case with **1**, the longer esters of **2** show the behavior described by eq 6 with *both* cyclodextrins. Reaction of the acetate of **2** is accelerated by α-CD but, unlike all other esters we have studied,[7,11] saturation kinetics (eq 2) were *not* observed; the rate increases are linear in [CD] up to 20 mM, with the second-order rate constant, k_2 = 0.71 M^{-1} s^{-1}. Thus, if there is any binding between the acetate of **2** and α-CD, it must be relatively weak (K_1 > 50 mM). The C4, C6, and C8 esters of **2** bind fairly strongly to α-CD, and their rates of cleavage show the presence of *two* cleavage processes, in accordance with eq 6 (Figure 4). With β-CD there are rate increases for the C2 and C4 esters of **2** that conform to simple saturation kinetics, while the C6 and C8 esters exhibit the more complex behavior described by eq 6 (Figure 5). Fitted constants for the esters **2** reacting with each CD are collected in Table III.

Discussion

The results reported above clearly implicate 1:1 *and* 2:1 binding, in some cases, and transition states for cleavage containing 1 *and* sometimes 2 molecules of a cyclodextrin. These different behaviors must be related to the alkyl chains of the esters **1** and **2** since for each series the aryl group remains constant. Therefore, before discussing our results in detail, we first comment on how substrates with alkyl chains interact with cyclodextrins.

The binding of various alkyl-bearing substrates to CDs is quite dependent on the chain length (and the head group), and in many cases there are good linear correlations of pK_1 (= $-\log K_1$) with N, the number of the carbons in the alkyl chain.[9,11] This is reasonable since the binding of guests to CDs is determined largely by two factors: the "size" of the included moiety and its hydrophobicity, both of which increase regularly with alkyl chain length.[19-22]

Binding of the esters **1** to α-CD shows a reasonable correlation (eq 7a) for the C3–C8 esters. The acetate is decidely off the line, probably because it binds differently. Likewise, for complexation with β-CD there is a fair correlation for the C3–C7 esters (eq 7b), with the octanoate seemingly being anomalous[23] (Figure 6). From

$$\alpha\text{-CD:} \quad pK_1 = (0.30 \pm 0.03)N + 1.28, \quad r = 0.975 \quad (7a)$$

$$\beta\text{-CD:} \quad pK_1 = (0.32 \pm 0.04)N + 1.75, \quad r = 0.976 \quad (7b)$$

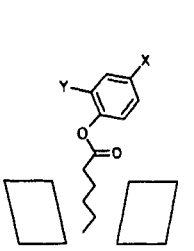
the slopes of the correlations, the two cyclodextrins have similar sensitivities to the alkyl chain length of the esters **1**, as is found with most substrates.[11] However, in general the sensitivity to N is quite dependent on the head group of the substrate, as discussed below.

With one exception,[23] the binding of the esters of **1** to β-CD is noticeably stronger than to α-CD (Tables I, II, and Figure 6), comparable to the behavior of other aryl–alkyl guests.[8,11] By contrast, *linear* alcohols (at least to C8),[8,24] alkanesulfonate anions (up to C7),[15] and alkanoate anions (up to C9)[25] bind to α-CD more strongly. Therefore, the nature of the head group of the alkyl-bearing guest influences the strength of binding, as well as its sensitivity to chain length.

The different complexing abilities of α- and β-CD must be attributable to the widths of their cavities (4.5 and 7.0 Å) since the depths (7.0 Å) are the same.[1] Space-filling molecular (CPK) models suggest a tight fit of *n*-alkyl chains in α-CD and a looser fit for β-CD. This suggestion is consistent with the behavior of linear alcohols, alkanesulfonate ions, and alkanoate ions, but with the aryl–alkyl guests (see above) there must be additional interactions with the aryl head groups, which favor complexation with β-CD. Most probably, it is simply that the phenyl ring of the guest helps to fill the wider, cone-shaped cavity of the β-CD host.

From the kinetics of the cleavage of the C3–C8 esters of **1** with α-CD, it is clear that 2:1 as well as 1:1 binding is important (eq 4, Figures 1 and 2). While the K_1 values decrease markedly (17 to 0.50 mM) and systematically with the alkyl chain length (eq 7a), the K_2 values for binding the second molecule of CD change little, and all lie in the range 10–30 mM, with most being near 20 mM (Table I).[17b] These values of K_1 and K_2 strongly suggest that the first binding involves inclusion of the alkanoate chain (**3**), while the second involves the aryl group (**4**).

At first sight it seems odd that 2:1 binding is not also evident for β-CD and the esters **1**, but two factors probably militate against it. Firstly, the 1:1 binding with β-CD is stronger and the esters of **1** can sit deeper in the wider CD cavity (**3**). Secondly, binding of a second molecule of β-CD to the exposed portion of the aryl group of **1** may be looser, also due to the wider cavity of the β-CD



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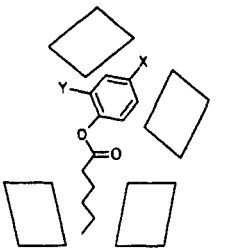

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(**4**). Nevertheless, as discussed later, it is very likely that *weak* 2:1 complexes are involved in the second-order cleavage process.

As with other aryl alkanoates,[11,26] the values of k_u for the hydrolysis of **1** and **2** (Tables I and II) show no significant dependence on the length of the acyl chain beyond C2 and C3. This behavior is normal for ester cleavage[26] in that steric effects are usually evident only for alkyl substitution α and β to the ester carbonyl group.[27] Thus, the 2-ethylhexanoate ester of **1** reacts about 25 times slower than the others (Table I). Such steric effects must be borne in mind when comparing the kinetic parameters for the cleavage of the C2 and C3 esters to those of the other esters. Comparisons between the parameters of the longer esters (C4–C8, 4MeC5) are most meaningful since their intrinsic reactivities (as expressed by k_u) are all essentially the same.

In discussing the effects of α- and β-CD on the cleavage of **1** and **2** we will make use of the kinetic parameters: k_c/k_u, k_2 (= k_c/K_1), and K_{TS}.[9,11] The ratio k_c/k_u denotes the limiting acceleration or retardation due to CD, and k_2 is the second-order rate constant for S + CD → P; it measures the reactivity of the CD toward different substrates under the reaction conditions.[28] The pseudoequilibrium constant, K_{TS}, is the *apparent* dissociation constant of the transition state of the CD-mediated reaction (symbolized as TS–CD) into the transition state of the normal reaction (TS) and CD (eq 8):

$$K_{TS} = \frac{[TS][CD]}{[TS\text{–}CD]} = \frac{k_u K_1}{k_c} = \frac{k_u}{k_2} \quad (8)$$

The derivation of eq 8 follows easily from the application of transition-state theory to k_u and k_c (or k_2).[29] The usefulness of K_{TS} is that pK_{TS} (= $-\log K_{TS}$) is directly proportional to the free energy of the stabilization of the transition state[30] due to the CD, regardless of the actual reaction mechanism. Thus, variations of pK_{TS} with structure may be used to probe transition-state structures and as a criterion of mechanism.[9,11]

The kinetic parameters which characterize the basic cleavage of the esters **1** (C4 to C8) by α-CD vary significantly with the alkyl chain length (Table I). There is a gradual change from retardation to acceleration (k_c/k_u = 0.48 to 3.4) and a large increase in the reactivity of α-CD toward the esters (k_2 = 1.7 to 150 M^{-1} s^{-1}). These systematic changes are due to a substantial

(19) Various properties related to hydrophobicity depend linearly on the number of carbons (N) in the chain of *n*-alkyl derivatives.[20-22] For example, for the transfer of aliphatic compounds (alkanes, alkenes, alcohols, alkanoic acids) from water to an organic phase (including micelles), the free energy change *per methylene group* is 0.6–0.9 kcal/mol, depending on the compound type.[20] Likewise, the Hansch hydrophobicity parameters, which are based on the partitioning of solutes between water and 1-octanol, increase monotonically with N,[21] with an incremental energy of ~0.7 kcal/mol per methylene. Also, the microhydrophobicity parameters introduced by Menger are essentially linear in N.[22]

(20) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; 2nd ed.; Wiley: New York, 1980; Chapters 2, 3, and 6.

(21) Hansch, C. *Drug Design* **1971**, *1*, 271. Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

(22) Menger, F. M.; Venkataram, U. V. *J. Am. Chem. Soc.* **1986**, *108*, 2980.

(23) Why the C8 ester is out of line with the others is not clear. It is conceivable that some kind of "saturation effect" is operating, whereby the depth of the CD cavity is reached so that no further improvement in K_1 or K_{TS} is possible.[15] Alternatively, it may be that the value of K_1 (and hence K_{TS}) is not accurately determined since, in the fitting, it is highly dependent on the curvature in the data at low [CD] (Figure 3, Table S2).

(24) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808.

(25) Ono, K.; Tokuda, M.; Murakami, K. *Polymer Reprints, Jpn.* **1979**, *28*, 1302.

(26) (a) Guthrie, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 897. *Can. J. Chem.* **1973**, *51*, 3494. (b) Tee, O. S.; Enos, J. A. *Can. J. Chem.* **1988**, *66*, 3027.

(27) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1940. Taft, R. W. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; Chapter 13.

(28) Note that in the case of ester cleavage k_2 increases with pH.[2a] However, while both k_c and k_u depend on pH, the ratio k_c/k_u does not and neither does K_1 (as long as experiments are carried out at pHs below the pK_a of the CD).[2,7] Therefore, K_{TS} (eq 8) is also independent of pH.

(29) In brief,[30] $k_u = \nu[TS]/[S]$, and $k_c = \nu[TS\text{–}CD]/[S\text{–}CD]$, where $\nu = k_B T/h$. Since $K_1 = [S][CD]/[S\text{–}CD]$ and also $k_2 = \nu[TS\text{–}CD]/[S][CD]$, then both parts of eq 8 follow.

(30) This approach was developed by Kurz: Kurz, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 987. It has been very influential in enzymology: Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10. Lienhard, G. E. *Science (Washington D.C.)* **1973**, *180*, 149. Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 219. Schowen, R. L. In *Transition States in Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum: New York, 1978; Chapter 2. Page, M. I. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; Chapter 1. Wolfenden, R.; Frick, L. In *Enzyme Mechanisms*; Page, M. I., Williams, A., Eds.; Royal Society of Chemistry: London, 1987; Chapter 7. Kraut, J. *Science (Washington D.C.)* **1988**, *242*, 533.

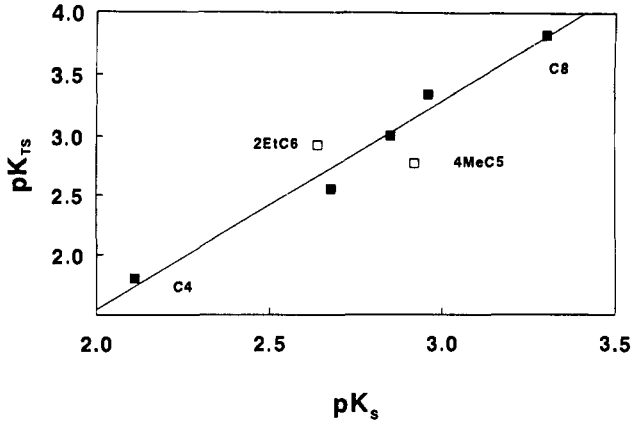
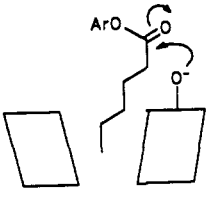


Figure 7. Correlation of transition-state binding (pK_{TS}) with substrate binding ($pK_s = pK_I$) for the reaction of α-CD with the C4–C8, 4MeC5, and 2EtC6 esters of **1**. The correlations line for the C4–C8 esters is expressed in eq 10.

increase in the stabilization of the transition state for esterolysis (K_{TS} = 16 to 0.15 mM) as the alkyl chain is lengthened by four carbons,[31] and they can be expressed in the form of a linear correlation (for N = 3–7):[32]

$$\alpha\text{-CD:} \quad pK_{TS} = (0.48 \pm 0.02)N + 0.49, \quad r = 0.989 \quad (9)$$

For reasons given earlier,[11] such correlations provide excellent evidence that esterolysis takes place when the alkyl chain of the ester is included in the CD cavity (**5**).



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Because of the correlations of pK_I (eq 7a) and pK_{TS} with N (eq 9), there is also a good correlation between these parameters for N = 3–7 (eq 10):

$$\alpha\text{-CD:} \quad pK_{TS} = (1.74 \pm 0.15)pK_I - 1.95, \quad r = 0.989 \quad (10)$$

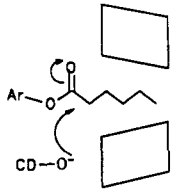
Furthermore, the points for the two branched (4MeC5 and 2EtC6) esters are not very far from the correlation line (Figure 7). Thus, the changes in the alkyl chains affect the binding of both the ester and its transition state in a similar manner, except that the transition-state binding is more sensitive. This is not unreasonable because of the more stringent geometric requirements that may be imposed by covalent interactions in the transition state for acyl transfer.

The correlation in eq 10 may be also viewed in a slightly different way. Lengthening the acyl chain of the ester significantly increases the strength of substrate binding (eq 7a). In the substrate–CD complexes that are formed, the ester functionality may sit progressively higher in the CD cavity, closer to the geometry of the transition state, so that the ester carbonyl is more easily attacked by an ionized hydroxyl group at the lip of the cavity (**5**).[33]

Therefore, two factors, both working in the same direction, serve to facilitate the reaction: transition-state stabilization through alkyl chain binding and a geometric factor positioning the ester group nearer to the attacking nucleophile. In consequence, the slope of the line in eq 10 is significantly greater than 1.

The behavior of the 1:1 complexes of **1** with β-CD are qualitatively similar to those with α-CD. As seen in Table II, values of k_c/k_u decrease and then increase with chain length. The rate constants k_2 are virtually constant for C3–C5 and then increase. Correspondingly, transition-state stabilization increases as K_{TS} values decrease; the value for the C8 ester may be somewhat inaccurate.[23] As seen also with α-CD (Table I), the extra methyl group in the 4MeC5 improves transition-state binding (relative to the C5 case), but with β-CD (Table II) the factor is larger, consistent with its wider cavity. In contrast, the 2-ethyl group of the 2EtC6 ester causes an increase in K_{TS}, implying that there is some destabilization relative to the C6 case due to an unfavorable steric interaction near the lip of the cavity.

As seen from the values of k_{c2}, the importance of the cleavage process involving *two* molecules of β-CD, tentatively ascribed to the process in eq 5, increases with the length of the C6, C7, and C8 esters of **1** (Table II). Also, the 4MeC5 ester has a reactivity comparable to that of the C6 ester and greater than that of the C5. Therefore, the binding of the alkyl chains of these esters affords a significant contribution to stabilization of the cleavage transition state. Viewed in terms of the process in eq 5, this could mean that with a longer alkyl chain the ester group sits higher in the β-CD cavity so that it is more easily attacked by an external nucleophile,[33] which in the present case is another molecule of β-CD (**6**).



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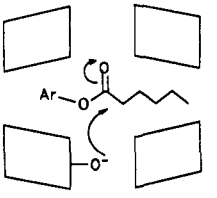

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In view of the 2:1 binding of α-CD with **1** discussed earlier, there is an alternative to the second-order cleavage process shown in eq 5 which should be considered: reaction via a discrete 2:1 complex (**7**). We note that k_c and k_{c2} for the long esters of **1** both increase with chain length and with similar sensitivities (Table II). In fact, the ratios k_c/k_{c2} are remarkably constant (45, 59, 49, and 48 mM) for the C6, C7, C8, and 4MeC5 esters. This means that the kinetic data for these esters, which clearly implicate two β-CD molecules at high [CD] (Figure 3), could easily be due to reaction within a ternary (2:1) complex:

$$\text{S–CD} + \text{CD} \underset{K_2}{\rightleftharpoons} \text{S–CD}_2 \xrightarrow{k_c'} \text{P} \quad (11)$$

If the process in eq 11 is operative, $k_{c2} = k_c'/K_2$, and assuming $K_2 \approx 50$ mM, the values of k_c' would be virtually the same as k_c for the 1:1 CD–ester complexes! Values of $K_2 \approx 50$ mM for β-CD are not unreasonable since they are ~20 mM for the narrower α-CD (Table I). However, since the increases in k^{obsd} are linear at high [CD] (Figure 3 and Table S2) and show no signs of saturation, any 2:1 binding of β-CD with **1** must be weak ($K_2 >$ 20 mM). Thus, it is quite possible that $K_2 > 50$ mM, in which case values of k_c' would be *greater* than k_c, meaning that the 2:1 β-CD–ester complexes would be *more* reactive than the 1:1 complexes! This type of situation may be the origin of the cooperative effects observed by Harada et al.[34] for ester cleavage brought about by CDs attached to polymer chains.

The rate constants k_{c2} may also be discussed using the Kurz approach.[9,30] In the same way that $K_{TS} = k_u/k_c$ (eq 8), $k_c/k_{c2} = K_{TS}' = [\text{TS–CD}][\text{CD}]/[\text{TS–CD}_2]$, where TS–CD is the tran-

(31) Note that the values of K_{TS} for the branched esters (2EtC6 and 4MeC5) are not markedly different from that of the hexanoate (Table 1).

(32) Since pK_{TS} increases linearly with N (eq 9), so do values of log k_2 (from eq 8 and since $k_u \approx$ constant). Thus, the selectivity of α-CD for the C4 to C8 esters increases monotonically with chain length, also.

(33) The normal reaction of esters with CDs involves nucleophilic attack of an ionized secondary hydroxyl on the carbonyl of a CD-bound ester.[2,8] In the discussion of eq 10, we argue that lengthening the acyl chain of the esters **1** facilitates this attack as the carbonyl groups of longer esters sit higher in the CD cavity. In a similar manner, such positioning could also facilitate attack by an external species.

(34) Harada, A.; Furue, M.; Nozakura, S. *Macromolecules* **1976**, *9*, 705.

sition state of the 1:1 cleavage process (eq 1b) and TS–CD_2 is the doubly-bound transition state corresponding to k_{c2}. Thus, K_{TS}' is a measure of the transition-state stabilization afforded by a second molecule of CD. According to this model, K_{TS}' is the same (~50 mM) for the C6, C7, C8, and 4MeC5 esters, consistent with the second CD molecule interacting only at the aryl end of the ester in the transition state (7). Therefore, regardless of whether discrete 2:1 substrate binding occurs (eq 11) and of the actual values of K_2 and k_c', the kinetic data can be interpreted in terms of a transition state having alkyl binding to one molecule of CD and aryl group binding to a second CD (7).

Assuming that the pathway in eq 11 is followed, why is it that α-CD does not also exhibit it? It must be because of the narrower cavity of α-CD and the different binding that results therefrom. Most likely it means that α-CD forms 2:1 complexes in which the longer esters of **1** are held too tightly[35] and in a geometry that is inappropriate for easy reaction, whereas the wider β-CD forms looser 2:1 complexes which have enough flexibility and access to the solvent for the reaction to occur.

Our data for the esters **2** are less extensive, so the trends are less clear. However, two features stand out: the lack of saturation kinetics for the cleavage of the acetate of **2** by α-CD and adherence to eq 6 for longer esters reacting with *both* CDs (Table III). The former means that binding of the acetate to α-CD is weak ($K_1 \gg 20$ mM) or nonexistent. Nevertheless, from the k_2 value we can evaluate K_{TS} = 15 mM, which is decidedly higher than that for cleavage of **1** acetate (5.3 mM). This difference is not due to electrostatic repulsion of the incoming nucleophile by the *o*-COO^- group of **2**, as this effect is present for k_u also and so should cancel out in $K_{TS} = k_u/k_c$ (eq 8). Rather, it must represent some added hindrance to transition-state formation, perhaps due to hydrogen bonding of the *o*-carboxylate group to secondary hydroxyls at the lip of the α-CD. However, such an effect is absent for β-CD as K_{TS} is virtually the same for the acetates of both **1** and **2** (2.2 and 2.9 mM).

The C4, C6, and C8 esters of **2** react with α-CD by both first- *and* second-order pathways (eq 6, Figure 4). Surprisingly, the kinetic parameters for the C4 and C6 esters are essentially equal *except* for k_{c2} (Table IIIa). The second-order process appears to be more efficient for the longer C6 ester, but it is no more efficient for the octanoate even though substrate binding of this ester is stronger. The ratios k_c/k_{c2} are reasonably constant (47, 32, 43 mM), again suggesting the formation of weak 2:1 complexes (see discussion of eq 11).

Trends for the reaction of **2** with β-CD are clearer and similar to those found for their isomers, **1**. For the C4, C6, and C8 esters, the strength of the 1:1 substrate binding increases with the alkyl chain length, as does the ease of cleavage (k_2 = 0.94 to 12 M^{-1} s^{-1}) and the transition-state stabilization (K_{TS} = 5.5–0.41 mM). In fact, there is a strong parallelism between the substrate and transition-state binding: a plot of pK_{TS} vs pK_1 has a slope of 1.11 (r = 0.968). Again, alkyl chain binding is involved in both the initial state and in the transition state for acyl transfer.[36]

For the process observed for the C6 and C8 esters of **2** reacting with two β-CD molecules, k_{c2} increases with the chain length, and the ratios k_c/k_{c2} are 110 and 63 mM, which may indicate weak 2:1 binding (see discussion of eq 11).

As we have seen, both **1** and **2** show processes involving *two* molecules of CD, either in substrate binding (eq 3) or in cleavage (eq 5 or eq 11). This raises the question of why such types of behavior were not seen previously with *p*-nitrophenyl alkanoate esters.[11,12] The primary difference between the three types of esters is the presence of the ionized carboxyl groups in **1** and **2**. Possibly, the presence of a strongly solvated carboxylate group holds the aryl groups of **1** and **2** sufficiently far out of the CD cavity that binding to and/or reaction with another CD molecule is possible. There may also be specific interactions between the carboxylate groups and hydroxyls at the lip of the CD cavity which favor geometries suitable for binding to a second CD. There may even be hydrogen bonding of the CD-bound ester carboxylate group to the second CD molecule.

Summary

The present work has revealed a surprising range of behaviors for the cleavage of two series of aryl alkanoate esters by α- and β-cyclodextrins. Depending on the ester, its acyl chain length, and the CD, the kinetics show rate acceleration (with or without saturation), retardation, acceleration and retardation, retardation and acceleration or two kinds of acceleration. In all but one case the esters show 1:1 binding with the CDs, and in one series there is also nonproductive 2:1 binding with α-CD. In many cases there are cleavage processes involving *two* molecules of CD which may well involve 2:1 (CD:ester) complexes, although the second CD must be only weakly bound. To the best of our knowledge such kinetic diversity has not been found previously for such simple substrates reacting with cyclodextrins, even though the 2:1 binding of CDs to dyes, surfactants, and fluorophores has frequently been reported.[1a,d,15b,38]

Clearly, the esters **1** and **2** have two quite distinct loci for binding: their alkyl chains and their aryl groups.[39] It is binding to these sites by the CDs, either singly or doubly, that leads to the variety of kinetic behavior reported in this paper.

Experimental Section

Materials. The cyclodextrins, acids, acid anhydrides, acid chlorides, and 4-hydroxy-3-nitrobenzoic acid (HNBA) were obtained from Aldrich. The esters **1** and **2** were synthesised by variations of literature methods.[40–42]

4-Carboxy-2-nitrophenyl esters (1, C2 to C5) were synthesized by the following procedure.[40] Sixty millimoles of the acid anhydride were added quickly to 10 mmol of HNBA (1.83 g) dissolved in 15.5 mL of 3 N aqueous NaOH with vigorous stirring. After 2–10 min, 1 N aqueous HCl was added until a precipitate appeared. The product was filtered off and washed with water. After recrystallization, the melting points were as follows: C2, 152–154 °C (lit.[43] 152 °C); C3, 142–143 °C; C4, 130–131 °C; C5, 122–123 °C.

C6 and C7 esters were prepared by combining HNBA (3.66 g, 20 mmol) with 40 mmol of anhydride and 5 drops of concentrated H_2SO_4 and heating at 85–90 °C.[41] After 4 h the mixture was cooled, and the product was filtered off and washed with a saturated aqueous $NaHCO_3$ solution and water. The melting points of the products were 89–90 °C and 76–77 °C (lit.[43] 75 °C), respectively.

C8 ester was prepared by combining HNBA (20 mmol) with the 90 mmol of the acid chloride in 30 mL of benzene and refluxing the mixture for 8 h. Solvent removal and recrystallization gave the desired ester, which melted at 68–69 °C.

2EtC6 ester was prepared from HNBA (15 mmol) with the acid chloride (15 mmol) in 20 mL of dry pyridine. After 9 h at 100 °C, the mixture was cooled and neutralized with a large volume of 1 M aqueous HCl. The solid material was recrystallized to give the ester melting at 59–62 °C.

(35) Linear alkanols bind more tightly to α-CD than to β-CD.[8,24]

(36) Even though there is alkyl group inclusion in the transition state, the group may not penetrate very far (**5**). We have obtained evidence that in the transition state for the cleavage of *p*-nitrophenyl acetate by β-CD the aryl group is largely *outside* the CD cavity. In particular, the cleavage of *p*-nitrophenyl acetate is not inhibited by various species.[37a] Likewise, the cleavage of *p*-nitrophenyl hexanoate is not inhibited by a series of alcohols, it is *catalyzed*, and saturation kinetics implicate ternary (ester–CD–ROH) complexes.[37b]

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4MeC5 ester was made as follows. 4-Methylpentanoic acid (1.74 g, 15 mmol), DCC (3.095 g, 15 mmol), and *p*-toluenesulfonic acid (150 mg) were dissolved in pyridine (3 mL) and benzene (50 mL). To the solution was added HNBA (2.75 g, 15 mmol), and the mixture was allowed to react for 4 days at room temperature.[42] The solvents were removed by evaporation, and the product was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ solution, and water. The residue was dissolved in acetone and filtered. Removal of the acetone gave a noncrystalline product.

2-Carboxy-4-nitrophenyl esters (2) were prepared from the acid anhydrides and 5-nitro-2-hydroxybenzoic acid (5-nitrosalicylic acid, Lancaster Synthesis), using either of the first two procedures outlined above. The melting points were as follows: C2, 159-162 °C; C4, 97-99 °C; C6, 90-92 °C.

The structures of all of the esters were confirmed by their proton NMR spectra and by the UV-vis spectral change that they gave on hydrolysis in aqueous base.

Kinetic Methods. Ester cleavage was followed spectrophotometrically using the same general approach and techniques as in earlier studies.[7,11,26b] The cleavages of **1** and **2** were monitored by the increases at 407 and 370 nm due to release of the dianions of the corresponding carboxynitrophenols. Initial substrate concentrations were 0.01-0.1 mM, depending on the solubility of the ester. Stock ester solutions were made up in methanol so that final solutions contained 0.1% (v/v) MeOH. The reaction medium was a 0.2 or 0.4 M phosphate buffer of pH 11.7, containing [CD] = 0-20 mM (see Tables S1-S3, supplementary material, for the actual concentrations). A high buffer capacity was used to avoid changes in pH caused by the ionization of the CD hydroxyl groups.[44] The observation cell was kept at 25 °C. Absorbance data points (100) were collected for 10 half-lives, and those covering 80-90% reaction gave good first-order behavior.

Fitting of the kinetic expressions (eqs 2, 4, and 6) was carried out with programs based on standard nonlinear least-square methods.[18] The value of k_u was fixed at the observed value, and the remaining constants were the parameters to be determined. In any case where there was little to choose between the qualities of the fits obtained with two different equations, the simpler of the two equations was chosen.[17]

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Registry No. 1 (C2), 1210-97-5; **1** (C3), 86868-06-6; **1** (C4), 56003-42-0; **1** (C5), 67880-44-8; **1** (C6), 65293-27-8; **1** (C7), 43049-38-3; **1** (C8), 113894-26-1; **1** (2E+C6), 137363-36-1; **1** (4MeC5), 137363-37-2; **2** (C2), 17336-14-0; **2** (C4), 93597-98-9; **2** (C6), 93598-00-6; **2** (C8), 115162-19-1; HNBA, 616-82-0; α-cyclodextrin, 10016-20-3; β-cyclodextrin, 7585-39-9; acetic anhydride, 108-24-7; propanoic anhydride, 123-62-6; butanoic anhydride, 106-31-0; pentanoic anhydride, 2082-59-9; hexanoic anhydride, 2051-49-2; heptanoic anhydride, 626-27-7; octanoyl chloride, 111-64-8; 2-ethylhexanoyl chloride, 760-67-8; 4-methylpentanoic acid, 646-07-1; 5-nitro-2-hydroxybenzoic acid, 96-97-9.

Supplementary Material Available: Tables of observed rate constants for the cleavage of 4-carboxyl-2-nitrophenyl and 2-carboxy-4-nitrophenyl alkanoates (**1** and **2**) as a function of the concentration of α- or β-cyclodextrins (Tables S1-S3) (9 pages). Ordering information is given on any current masthead page.

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Hydrogen Bonds to Carboxylate Groups. Syn/Anti Distributions and Steric Effects

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Abstract: The syn/anti distribution for hydrogen bonds to small-molecule carboxylate groups has been analyzed. The data set used consisted of 15 acetate structures, 48 primary carboxylates, 172 secondary carboxylates, and 20 ternary carboxylates retrieved from the Cambridge Structural Database. For 876 interactions there is overall a slight preference for syn geometry with a clear correlation between the syn/anti ratio and steric hindrance in the anti positions between the donor and substituents on the acceptor molecule. In the absence of steric interference, syn H-bonds are not significantly preferred according to statistics. It is shown that the stereoelectronic preferences for catalysis by carboxylate groups do not translate into stereoelectronic preferences for hydrogen-bond formation.

Introduction

The question of stereoelectronic preferences for catalysis by carboxylate groups has received detailed attention from mechanistic, structural, and functional perspectives.[1-4] Gandour used the equilibria for deprotonation of the syn and anti conformation of simple carboxylic acids to show that syn lone pairs are $>10^4$ times more basic than anti lone pairs ($K_a' > 10^4$ larger than K_a).[1] Hence, in biologically active systems, a syn lone pair of a carboxylate group is catalytically more active than the anti lone pair.[5]

Our research interests have focused on the forces that affect molecular association and preorganization of hydrogen-bonded aggregates, whether or not such aggregates are reactive or show catalytic behavior.[6] Carboxylate groups, like other hydrogen-bonding groups, can play just as important a role as a site for directing molecular organization of catalytic components as they do in actually promoting catalysis. Here we seek to decouple the organizational properties of carboxylate groups from their reactivity properties and, in the process, to address the question of whether stereoelectronic preferences are similar for the two very different roles that carboxylate groups assume. Using data from

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