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Cooperative Behavior by Two Different Cyclodextrins in a Reaction: Evidence of Bimodal Transition State Binding

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By virtue of their binding ability, cyclodextrins[1] (CDs) can affect organic reactions in many interesting ways.[1−3] In previous work[4] we found several cases where the basic cleavage of an aryl ester is mediated by two molecules of a CD, with one molecule binding to the acyl group of the ester and the other to its aryloxy group in the transition state. Following these observations, we speculated about reactions mediated by *two different* cyclodextrins, acting in cooperation. Obviously, observation of the phenomenon would require a judicious choice of substrate and CDs, so that its effect was clearly distinguishable from the combined effects of the two CDs acting independently. Here we present results for an ester cleavage by two different CDs, in which their combined effect significantly exceeds the sum of their individual effects, thereby providing clear-cut evidence of cooperative behavior.

Using earlier work on the cleavage of aryl alkanoates by CDs[3−7] for guidance, we have carried out kinetic studies of this reaction in the presence of pairs of CDs.[8] Initial experiments on several aryl esters[9] reacting with 10 mM α-CD[1] and 5 mM β-CD[1] were inconclusive. More detailed studies of the basic cleavage of *p*-nitrophenyl hexanoate (*p*NPH) and of 2-naphthyl acetate by mixtures of α-CD and β-CD (0−10 mM) simply showed that the two CDs act individually. Results for the reaction of *p*NPH with α-CD and γ-CD[1] (0−20 mM) were more promising, showing reactivities up to 28% greater than calculated for independent action of the two CDs. For analogous experiments with *p*-nitrophenyl octanoate (*p*NPO) + α-CD + γ-CD, the effects were larger, with enhancements up to 43%, but the analysis was complicated by nonproductive 2:1 (CD:ester) binding by α-CD at high [CD]. Most convincing are our experiments for *p*NPO reacting in the presence of dimethyl-β-cyclodextrin (dm-β-CD)[1b] and γ-CD,[10] where the cleavage was substantially more rapid than expected for the two CDs behaving independently. The data clearly show evidence of a third-order process (Figure 1), despite the complication of 2:1 binding by dm-β-CD.

Figure 1a presents the observed rate constants (k^{obsd}) for the cleavage of *p*NPO in 20 mixtures of dm-β-CD and γ-CD, plotted against those calculated (k^{calcd}) for the two CDs reacting independently. It clearly shows large *positive* deviations of up to 143%. This enhanced reactivity is quantitatively explained by a third-order reaction involving the ester and *both* CDs. Figure 1b shows the analogous plot, where now the values of k^{calcd} include a contribution from this third-order process which accounts for ~70% of the reaction flux at the highest [dm-β-CD][γ-CD].

Our analysis is as follows. Based on many previous studies,[3−7] we allow for hydrolysis in the basic medium (eq 1) and for reaction with each of the CDs, CD and CD′ (eqs 2 and 2′). In simple cases, where there is no cooperativity (and no 2:1 binding), these three processes suffice to explain the data. With the high [CD] used, it turned out that nonproductive 2:1 binding (eq 3) is significant also. Lastly, the enhanced reactivity evident in Figure 1a is ascribed to a third-order process (eq 4).

$$\mathrm{S} \xrightarrow{k_u} \text{products} \tag{1}$$

$$\mathrm{S} + \mathrm{CD} \underset{K_1}{\rightleftharpoons} \mathrm{S{-}CD} \xrightarrow{k_c} \text{products} \tag{2}$$

$$\mathrm{S} + \mathrm{CD'} \underset{K_1'}{\rightleftharpoons} \mathrm{S{-}CD'} \xrightarrow{k_c'} \text{products} \tag{2′}$$

$$\mathrm{S{-}CD} + \mathrm{CD} \underset{K_2}{\rightleftharpoons} \mathrm{S{-}CD_2} \tag{3}$$

$$\mathrm{S} + \mathrm{CD} + \mathrm{CD'} \xrightarrow{k_3} \text{products} \tag{4}$$

$$k^{\mathrm{obsd}} = \frac{(k_uK_1K_1' + k_cK_1'[\mathrm{CD}] + k_c'K_1[\mathrm{CD'}] + k_3K_1K_1'[\mathrm{CD}][\mathrm{CD'}])K_2}{(K_1K_2K_1' + K_2K_1'[\mathrm{CD}] + K_1K_2[\mathrm{CD'}] + K_1'[\mathrm{CD}]^2)} \tag{5}$$

The five processes in eqs 1−4 lead to the expression in eq 5, which looks unwieldy but is not since all of the constants except k_3 were determined from separate experiments with CD and CD′, run at the same time (see Table S1 of the supplementary material and Table 1, where CD = dm-β-CD and CD′ = γ-CD). These six constants, and eq 5, without the k_3 term, were used to find the values of k^{calcd} which take into account the two CDs acting independently (Figure 1a). To find k_3, we analyzed ($k^{\mathrm{obsd}} - k^{\mathrm{calcd}}$) against [CD][CD′]/*D*, where *D* is the denominator of eq 5. From the slope of the *linear* plot ($= k_3K_1K_1'K_2$), we get $k_3 = 15\,100 \pm 900\ \mathrm{M^{-2}\ s^{-1}}$, which was used in eq 5 to generate the graph in Figure 1b.[11]

For the third-order process (eq 4), we propose a termolecular transition state in which the dm-β-CD binds the acyl group of *p*NPO and γ-CD binds its aryloxy group (Chart 1). At this point we cannot be sure which CD actually attacks the ester, but we believe it to be γ-CD. Consistent with this belief, the apparent dissociation constant (K_{TS}) for release of γ-CD from the transition state[3] of the k_3 process is 2.7 mM, close to 1.4

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(8) Reactions were studied using stopped-flow UV−vis spectrophotometry.[4,5,7] For the experiments with two CDs, one syringe contained ester + one CD in water, and the other had the second CD + buffer. The medium was a phosphate buffer of pH 11.6 (0.2 M after mixing).[4−7]

(9) *p*-Nitrophenyl hexanoate, octanoate, and decanoate; *m*-nitrophenyl hexanoate and octanoate; and 1- and 2-naphthyl acetates.

(10) These reactants were selected because dm-β-CD and γ-CD show contrasting behaviors with aryl alkanoates like *p*NPO.[5] Specifically, dm-β-CD binds strongly to the acyl groups of the esters and it retards their cleavage, whereas γ-CD binds more weakly to their aryl groups and speeds up cleavage (see Table S1). Also, numerical simulations using known parameters[5] suggested that a third-order process involving these two CDs might be more easily discernible relative to the competing second-order processes.

(11) (a) Significant formation of a ternary complex {CD−ester−CD′} would give a nonlinear dependence of ($k^{\mathrm{obsd}} - k^{\mathrm{calcd}}$) on [CD][CD′]/*D* (downward curvature). It is likely that one is formed, but not in high enough concentration to affect the kinetics. (b) Our data for *p*NPO reacting with α-CD *and* γ-CD also analyze well by this approach (Table S2), yielding a value of $k_3 = 32\,000 \pm 1300\ \mathrm{M^{-2}\ s^{-1}}$. The present values of k_3 are comparable to but larger than $k_3 = 4400\ \mathrm{M^{-2}\ s^{-1}}$ for *p*NPO reacting with two molecules of hydroxypropyl-β-CD.[4c]

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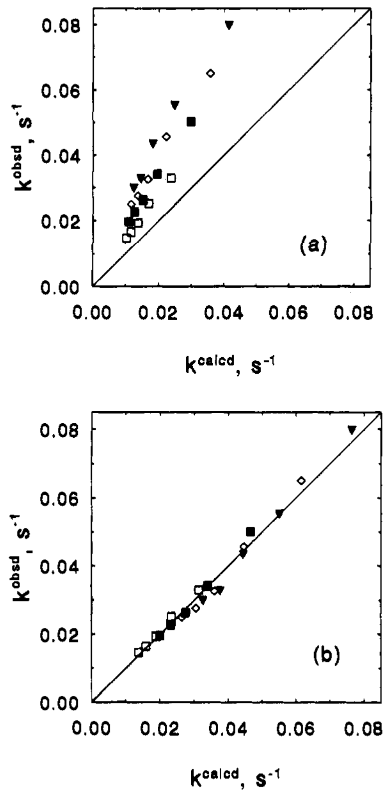


Figure 1. Plots of k^{obsd} against k^{calcd} for the basic cleavage of *p*NPO in the presence of dm-β-CD and γ-CD, for two kinetic models, with and without a third-order process. The actual data are given in Table S1. The symbols are for different [γ-CD] (in mM): = □, 5; ■, 10; ◇, 15; and ▼, 20. For each of these, [dm-β-CD] = 4, 8, 12, 16, and 20 mM. (a) For k^{calcd}, calculated assuming the processes in eqs 1-3 but no third-order process. (b) For k^{calcd} including the third-order process involving *p*NPO and both CDs (eq 4, k_3 = 15 100 M^{-2} s^{-1}). This plot has a correlation coefficient of 0.994 (for 20 points).

mM for the second-order reaction of *p*NPO with γ-CD alone. By contrast, for the dissocation of dm-β-CD from the termolecular transition state, K_{TS} is 8.2 mM, 17 times greater than 0.47 mM for the reaction of *p*NPO with dm-β-CD alone (from the data in Table 1). Likewise, the parameters for the cleavage of *p*NPO by α-CD and γ-CD are more consistent with acyl inclusion by α-CD and reaction with γ-CD.

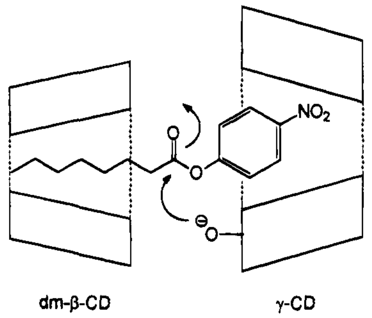
In summary, we have strong evidence for a reaction mediated by two different cyclodextrins acting in cooperation by bimodal recognition of different parts of the substrate. The benefit of the second CD may result from sequestering of the alkanoate ester chain, thereby reducing unfavorable hydrophobic interactions. Presumably, if the two CDs were joined together with a suitable spacer,[12] one would have a reactive host with two distinct recognition sites, capable of selective esterolysis.[13]

Table 1. Constants for the Basic Cleavage of *p*-Nitrophenyl Octanoate in the Presence of Dimethyl-β-cyclodextrin and γ-Cyclodextrin[a]

const	units	CD	value
k_u	s^{-1}	none	0.0585
k_c	s^{-1}	dm-β-CD	0.0202 ± 0.0008
K_1	mM	dm-β-CD	0.162 ± 0.017
K_2	mM	dm-β-CD	16.8 ± 1.6
k_c'	s^{-1}	γ-CD	0.605 ± 0.087
K_1'	mM	γ-CD	15.0 ± 4.6
k_3	M^{-2}s^{-1}	dm-β-CD + γ-CD	15 100 ± 900

[a] In an aqueous phosphate buffer of pH 11.6, at 25 °C. Based on the data in Table S1. The constants k_c, K_1, and K_2 were obtained from the variation of k^{obsd} with [dm-β-CD] = 0, 0.5, 1, 2, 4, 8, 12, 16, and 20 mM, in the normal way.[4,5,7] Likewise, k_c' and K_1' were found from kinetic runs with [γ-CD] = 0, 5, 10, 15, and 20 mM. The values of these constants agree well with those from previous experiments. The origin of k_3 is given in the text. The uncertainties are the standard errors from least-squares analysis.

Chart 1. Proposed Termolecular Transition State



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Supplementary Material Available: Tables of observed and calculated rate constants for the cleavage of *p*NPO in the presence of dm-β-CD and γ-CD and of α-CD and γ-CD (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(12) For example see: Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1993**, *115*, 9353 and references therein.

(13) Two groups have made catalysts from two β-CDs joined together on their primary sides by a catalytic spacer: Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1992**, *114*, 5882. Aiike, T.; Nagano, Y.; Yamamoto, Y.; Nakamura, A.; Ikeda, H.; Ueno, H.; Toda, F. *Chem. Lett.* **1994**, 1089.