Catalysis of Ester Aminolysis by Cyclodextrins. The Reaction of Alkylamines with *p*-Nitrophenyl Alkanoates†

Timothy A. Gadosy, Michael J. Boyd, and Oswald S. Tee*

Department of Chemistry and Biochemistry, Concordia University, Montréal, Québec, Canada H3G 1M8

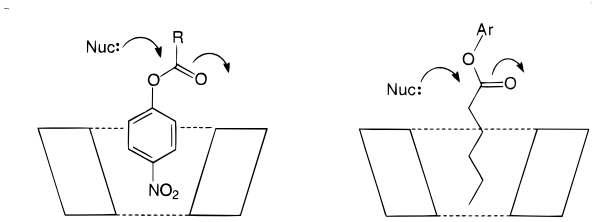
Received December 28, 1999

The effects of four cyclodextrins (α-CD, *β*-CD, hydroxypropyl-*β*-CD, and *γ*-CD) on the aminolysis of *p*-nitrophenyl alkanoates (acetate to heptanoate) by primary amines (*n*-propyl to *n*-octyl, isobutyl, isopentyl, cyclopentyl, cyclohexyl, benzyl) in aqueous solution have been investigated. Rate constants for amine attack on the free and CD-bound esters (k_N and k_{cN}) have ratios (k_{cN}/k_N) varying from 0.08 (retardation) to 180 (catalysis). For the kinetically equivalent process of free ester reacting with CD-bound amine (k_{Nc}), the ratios k_{Nc}/k_N vary from 0.2 to 28. Either way, there is evidence of catalysis in some cases and retardation in others. Changes in reactivity parameters with structure indicate more than one mode of transition state binding to the CDs. Short esters react with short alkylamines by attack of free amine on the ester bound by its aryl group, but for longer amines, free ester reacts with CD-bound amine. Reaction of long esters with long amines, which is catalyzed by *β*-CD and *γ*-CD, involves inclusion of the alkylamino group and possibly the ester acyl group. The larger cavity of *γ*-CD may allow the inclusion of the ester aryl group, as well as the alkylamino group, in the transition state. Reaction between an ester bound to the CD by its acyl group and free amine appears not to be important.

Introduction

Cyclodextrins (CDs) form inclusion complexes with a wide variety of species in aqueous solution.[1] As a result they have effects on the rates of organic reactions, ranging from complete inhibition through mild retardation to significant catalysis, depending on the reaction and the CD.[1−3] These features have been observed for basic ester cleavage in the presence of CDs, which has been investigated by many groups,[2−4] including ours.[5−8] By contrast, the effect of CDs on the reactions of esters with nucleophiles besides hydroxide ion have received little attention. It was reported that nucleophilic attack of α-amino acid anions on *p*-nitrophenyl acetate (pNPA) can be catalyzed by CDs,[9a] but a later study in our laboratory showed that the catalytic effect is less than originally thought.[9b]

In view of the limited amount of earlier work, we have undertaken detailed studies of the effects of cyclodextrins on the attack of several nucleophiles on alkanoate esters.[10] Our first studies involved nucleophiles that do not bind significantly to CDs to see how binding the esters to CDs affects their reactivity. For the reactions of hydroxylamine, imidazole, and the anions of 2,2,2-trifluoroethanol (TFE) and 2-mercaptoethanol (2-ME) with pNPA and *p*-nitrophenyl hexanoate (pNPH) in the presence of CDs, it was found that the CD-bound esters have the same or slightly reduced reactivities as the free esters, suggesting that the carbonyl groups of esters bound to CDs are fairly accessible to the nucleophiles in the medium.[10a] However, from this initial study it was not possible to discern the mode of binding of the ester during attack by the nucleophile. From previous studies,[7,8a] it seemed likely that pNPA would react with inclusion of its aryl group in the CD cavity, as in **1**, whereas pNPH might well react with acyl group inclusion, as in **2**.



1 **2**

To distinguish between the modes **1** and **2**, we studied the attack of the anions of TFE and 2-ME on a series of

* To whom correspondence should be addressed. Telephone: +1 (514) 848-3348. FAX: +1 (514) 848-2868. E-mail: ostee@vax2.concordia.ca.

† Based partly on the Ph.D. thesis of T. A. Gadosy (Concordia University, Montreal Canada, 1995).

(1) (a) Bender, M.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag, New York, 1978. (b) Szejtli, J. *Cyclodextrins and their Inclusion Complexes*; Akademiai Kiado, Budapest, 1982. (c) Szejtli, J. *Carbohyd. Polym.* **1990**, *12*, 375. (d) Various aspects of cyclodextrin chemistry have recently been reviewed by multiple authors in a special issue of *Chemical Reviews*: *Chem. Rev.* **1998**, *98* (5), 1741−2076.

(2) Komiyama, M.; Bender, M. L. In *The Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; Chapter 14.

(3) Tee, O. S. *Adv. Phys. Org. Chem.* **1994**, *29*, 1.

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

(5) Tee, O. S.; Takasaki, B. K. *Can. J. Chem.* **1985**, *63*, 3540.

(6) (a) Tee, O. S., Bozzi, M.; Hoeven, J. J.; Gadosy, T. A. *J. Am. Chem. Soc.* **1993**, *115*, 8990. (b) Tee, O. S.; Bozzi, M.; Clement, N.; Gadosy, T. A. *J. Org. Chem.* **1995**, *60*, 3509. (c) Gadosy, T. A.; Tee, O. S. *Can. J. Chem.* **1996**, *74*, 745.

(7) (a) Tee, O. S.; Mazza, C.; Du, X.-X. *J. Org. Chem.* **1990**, *55*, 3603. (b) Tee, O. S.; Du, X.-X. *J. Am. Chem. Soc.* **1992**, *114*, 620. (c) Tee, O. S.; Giorgi, J. B. *J. Chem. Soc., Perkin Trans.* **2 1997**, 1013.

(8) (a) Gadosy, T. A.; Tee, O. S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 715; *J. Chem. Soc., Perkin Trans. 2* 1994, 2069. (b) Tee, O. S.; Gadosy, T. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2191. (c) Tee, O. S.; Boyd, M. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1237. (d) Tee, O. S.; Giorgi, J. B. *J. Am. Chem. Soc.* **1995**, *117*, 3633.

(9) (a) Barra, M.; de Rossi, R. H. *Can. J. Chem.* **1991**, *69*, 1124. (b) Tee, O. S.; Gadosy, T. A.; Giorgi, J. B. *Can. J. Chem.* **1997**, *75*, 83.

(10) (a) Tee, O. S.; Gadosy, T. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2307. (b) Gadosy, T. A.; Tee, O. S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 71.

10.1021/jo9919660 CCC: $19.00
Published on Web 09/27/2000

p-nitrophenyl alkanoates (C_2 to C_{10}) in the presence of α-CD, *β*-CD, and hp-*β*-CD.[10b,11] On the basis of previous studies of reactions of alkyl derivatives in the presence of CDs,[3,7,8,12,13] and on the binding of aliphatics to CDs,[3,4,14,15] we used the sensitivity of kinetic parameters for the CD-mediated reactions to ester chain length to probe for acyl group binding in the transition state. It was found that for short esters (C_2 to C_6) the parameters are not sensitive to the acyl chain, but for longer esters they increase strongly with the chain length.[10b] This behavior was taken to mean (i) short esters that bind to the CD by aryl inclusion react through aryl group inclusion (**1**); (ii) short esters that bind by acyl inclusion[7b,8a] have their carbonyl groups buried in the CD cavity so that the dominant acyl-bound complexes must first isomerize to less stable, aryl-bound complexes before reaction occurs through **1**; (iii) for longer alkanoates, the carbonyl groups of their acyl-bound forms are exposed enough to the medium that nucleophilic attack takes place on the predominant acyl-bound forms (**2**).[10b]

Following studies with nonbinding nucleophiles,[10] we have turned our attention to ester cleavage by primary amines which bind to CDs.[14b] Here we report extensive studies of the reaction of *p*-nitrophenyl alkanoates with simple alkylamines in the presence of α-CD, *β*-CD, hp-*β*-CD, and *γ*-CD. These CDs differ in their cavity sizes[11] and hence in their abilities to bind organic guests.[1,3,4,10,14,15] The intent was to establish CD-mediated aminolysis and to find out how it varies with the binding abilities of the amine and the ester in order to probe the importance of inclusion of the two reactants during the reaction. Differences arising from the CD cavity sizes[11] were also of interest since a larger CD cavity might permit partial inclusion of both reactants in the transition state. As previously, the sensitivity of kinetic parameters to chain length would serve as the main criterion of transition state binding,[3,7,8,10b,12,13] along with appropriate comparisons to initial state binding parameters.

Results

The present studies were more demanding than previous ones[10] because of the necessity to take account of the binding of both substrates to cyclodextrins. However, we took advantage of previous studies of ester cleavage to provide dissociation constants for the {ester·CD} complexes,[6−8] obtained under the same basic conditions (pH 11.6). These constants (K_S) are given later in tables that present kinetic results. Most of the dissociation constants for the {amine·CD} complexes formed by *β*-CD and hp-*β*-CD were available from recent studies[14b] carried out expressly as preparation for work on aminolysis. The remaining constants were determined by various methods described in the Experimental Section, as the need arose. All of the dissociation constants for {amine·CD} complexes (K_N) are collected in Table 1, and those for the *n*-alkylamines are plotted in Figure 1 in the form of pK_N (= −log K_N) against the alkyl chain length, *n*.

Table 1. Dissociation Constants (K_N) of Complexes Formed from Amines and CDs[a]

amine	α-CD	*β*-CD[b]	hp-*β*-CD[b]	*γ*-CD
n-propyl	46.6 ± 5.9	108	141	149 ± 17
n-butyl	13.3 ± 1.1	35.6[c]	42.2[c]	65.6 ± 3.2
n-pentyl	3.08 ± 0.54	11.4[c]	13.7[c]	19.5 ± 2.8
n-hexyl	1.60 ± 0.12	2.62	4.81	9.29 ± 0.28
n-heptyl	0.431 ± 0.128	0.955	1.32	2.84 ± 0.37
n-octyl	0.134[d]	0.273[d]	0.519	1.12[d]
isobutyl		16.2 ± 1.9[e]	36.1 ± 2.7[e]	
isopentyl		5.81 ± 0.17[e]		
cyclopentyl		13.5	16.1	
cyclohexyl		1.83	5.21[f]	
benzyl		14.5 ± 1.3[e]	14.7 ± 0.9[e]	

[a] Values of K_N in mM, determined at 25 °C, in an aqueous buffer of pH 11.60. At this pH, the amines are ∼90% in their free base forms ($pK_a \approx 10.6$), except for benzylamine ($pK_a = 9.35$).[17] For the more soluble amines (*n*-propyl, *n*-butyl, *n*-pentyl, cyclopentyl, and cyclohexyl), the buffer was made from the amine whereas for the others a 0.2 M phosphate buffer was used. The dissociation constants that are presented with errors were determined in the present work, as described in the Experimental Section. [b] The values for *β*-CD and hp-*β*-CD without errors are from a prior study that used the displacement of a fluorescent probe,[14b] [c] Using the competition between amines and phenolphthalein for *β*-CD, we obtained very similar values of 38.4 ± 1.2 mM and 10.9 ± 0.6 mM for *n*-butylamine and *n*-pentylamine, respectively, whereas for hp-*β*-CD and the same two amines, the agreement was not quite as good: 64.7 ± 2.7 mM and 17.1 ± 0.9 mM, respectively. [d] Obtained by extrapolation of the linear relationship between pK_N and chain length (Figure 1) because attempts to measure K_N were not successful, due to the low solubility of the amine and/or the amine·CD complex. [e] Determined by competition with phenolphthalein (see Experimental Section). [f] This value for cyclohexylamine is somewhat suspect (see Table 3, footnote b, and the Experimental Section).

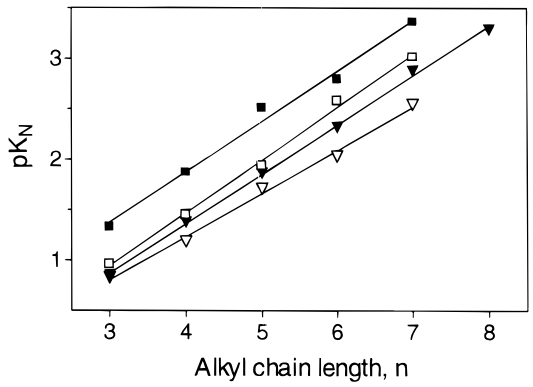


Figure 1. Chain length dependence of dissociation constants, plotted as $pK_N = -\log K_N$, for the binding of primary *n*-alkylamines to cyclodextrins, from the data from Table 1. The symbols are: ■, α-CD; □, *β*-CD; ▼, hp-*β*-CD; ▽, *γ*-CD.

There are two main features to note about the values of K_N. First, for a given amine the strength of binding follows the order: α-CD > *β*-CD ∼ hp-*β*-CD > *γ*-CD, as expected from the relative sizes of the CD cavities[11] since alkyl chains fit snugly in α-CD, less snugly in *β*-CD (and hp-*β*-CD), and even less so in *γ*-CD.[1,14,15] Second, the strength of binding of the *n*-alkylamines increases monotonically with the chain length (Figure 1), as found with many derivatives.[3,4,7,8,14,15] Somewhat surprisingly, the

(11) α-CD has 6 glucose units joined in a torus, *β*-CD has 7, and *γ*-CD has 8. Thus, their cavities differ appreciably in width (∼6, ∼8, and ∼10 Å, respectively) but not in depth (∼8 Å).[1] "Hydroxypropyl-*β*-cyclodextrin" (hp-*β*-CD) is *β*-CD in which most of the primary hydroxy groups have been modified by 2-hydroxypropyl groups,[1c,e] so the width of its cavity is close to that of *β*-CD but its depth may be altered.

(12) Bonora, G. M.; Fornasier, R.; Scrimin, P.; Tonellato, U. *J. Chem. Soc., Perkin Trans. 2* **1985**, 367.

(13) Tee, O. S.; Iyenger, N. R.; Takasaki, B. K. *Can. J. Chem.* **1993**, *71*, 2139.

(14) (a) Tee, O. S.; Gadosy, T. A.; Giorgi, J. B. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1705. (b) Tee, O. S.; Gadosy, T. A.; Giorgi, J. B. *Can. J. Chem.* **1996**, 74, 736. (c) Tee, O. S.; Fedortchenko, A. A.; Loncke, P. G.; Gadosy, T. A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1243.

(15) (a) Matsui, Y.; Mochida, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2808. (b) Satake, I.; Ikenoue, T.; Takashita, T.; Hayakawa, K.; Meda, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2746. (c) Satake, I.; Yoshida, S.; Hayakawa, K.; Meda, T.; Kusumoto, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3991. (d) Park, J. W.; Song, H. J. *J. Phys. Chem.* **1989**, *93*, 6454.

slopes of the plots for the four CDs are very close (0.50, 0.52, 0.49, 0.43), indicating virtually the same sensitivity to chain length. We take these to mean that even if the fit of an alkyl chain in a CD is not particularly snug, as is conceivably the case with β-CD and γ-CD,[15e] the alkyl chain adheres to the interior surface of the CD cavity or that one or more of the glucose moieties of the two larger CDs can tilt inward to provide a comparable "grip" on the chain. In addition, a referee has suggested that the almost constant slopes may reflect the similar extents to which the amines must be desolvated to be included in a CD. Regardless of its origin, there is a distinct sensitivity of the strength of amine binding to the alkyl chain, so that chain length dependence may be used as a probe of alkylamine inclusion in the transition state for aminolysis. Also, the linearity of the plots of pK_N against n (Figure 1) allowed us to estimate K_N values for *n*-octylamine in three cases where they were not readily measured.[16]

We have carried out two distinct series of kinetics experiments on CD-mediated aminolysis. First, we studied the cleavage of *p*-nitrophenyl acetate (pNPA) and *p*-nitrophenyl hexanoate (pNPH) by various amines in the presence of α-CD, β-CD, hp-β-CD, and γ-CD. Second, we looked at the reaction of a series of *p*-nitrophenyl alkanoates with *n*-heptylamine, in the presence of the same CDs. As previously,[10] the reaction medium was a basic buffer of pH 11.6, in which the alkylamines ($pK_a \sim 10.6$)[17] are present largely in their free base forms.

As in earlier studies,[9b,10] analysis of the kinetic data was based on consideration of four processes: hydrolysis of the ester (S) in the medium (eq 1); ester cleavage through an {ester·CD} complex (eq 2); reaction of the free ester with the nucleophile (Nuc) (eq 3); reaction of the {ester·CD} complex with free Nuc (eq 4).[18] For these four reactions, and the condition that $[S{\cdot}CD] < [S]_0 \ll [CD]_0$, the expected variation of k_{obsd} with [Nuc] and [CD] is given by eq 5.

$$S \xrightarrow{k_u} \text{products} \quad (1)$$

$$S + CD \underset{K_S}{\rightleftharpoons} S{\cdot}CD \xrightarrow{k_c} \text{products} \quad (2)$$

$$S + Nuc \xrightarrow{k_N} \text{products} \quad (3)$$

$$S{\cdot}CD + Nuc \xrightarrow{k_{cN}} \text{products} \quad (4)$$

$$k_{obsd} = \frac{(k_u K_S + k_c[CD]) + (k_N K_S + k_{cN}[CD])[Nuc]}{(K_S + [CD])} \quad (5)$$

Equation 5 gave good descriptions of the data in previous studies,[9b,10] and it works well for aminolysis also, as shown by the detailed example in Figure 2. However, because eq 5 is nonlinear and bivariate, it is not easily used in analysis and so we convert it to the linear form

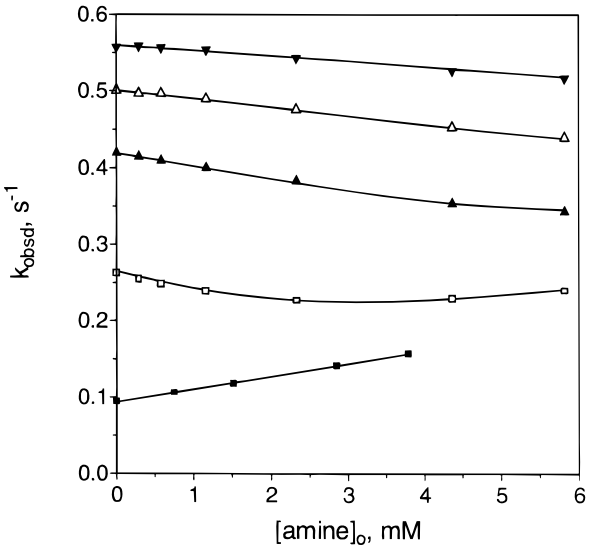


Figure 2. Rate constants for the reaction of *p*-nitrophenyl acetate with *n*-heptylamine, with and without β-CD. The symbols for different $[CD]_o$ are as follows: ■, none; □, 2.00; ▲, 5.02; △, 7.50; ▼, 10.00 mM. The curves are calculated from eq 5, using fitted constants[20] obtained from multiple linear regression analysis in terms of eq 6.

in eq 6 by dividing through by $f_S = K_S/(K_S + [CD])$. For values of k_{obsd} obtained at various $[CD]_o$ and $[Nuc]_o$, eq 6 is used to analyze the results by multiple linear regression,[19] from which we obtain the constant k_{cN} for reaction of the nucleophile with CD-bound ester (eq 4). Note that in the present work one must take account of the binding of the amine nucleophile to the CD (eq 7) because it affects the values of [CD] and [Nuc] that are used in the analysis. Details of their calculation are given in the Experimental Section. A value of k_N can be obtained from the multiple regression, but we prefer the more accurate value obtained from the variation of k_{obsd} with $[Nuc]_o$ in absence of CD, when $k_{obsd} = k_u + k_N[Nuc]_o$.

$$k_{obsd}/f_S = k_u + k_N[Nuc] + k_c[CD]/K_S + k_{cN}[Nuc][CD]/K_S \quad (6)$$

$$CD + Nuc \overset{K_N}{\rightleftharpoons} CD{\cdot}Nuc \quad (7)$$

The data shown in Figure 2 are for the reaction of pNPA with *n*-heptylamine in the presence of β-CD for 5 different $[CD]_o$ and various $[amine]_o = [Nuc]_o$. Multiple linear regression of all 33 data points in terms of eq 6 gave an excellent correlation and fitted constants[20] which were used to generate the curves in the figure. This case was carried out in detail, as were others previously,[9b] to firmly establish the validity of the treatment, especially for an amine used at low concentrations because of its poor solubility in water. For the remaining cases, fewer measurements were made, as detailed later.

At first glance, the data in Figure 2 are puzzling, because k_{obsd} decreases with $[amine]_o$, when the CD is

(16) There is a strong correlation between pK_N values for the binding of *n*-alkylamines to β-CD and the analogous values for *n*-alkyl alcohols[4,15a] ($r = 0.997$), with near unit slope ($= 0.92 \pm 0.04$). Moreover, the points for isobutyl, isopentyl, and cyclohexyl are very close to the correlation line, and the point for cyclopentyl is only 0.4 p*K* units away.

(17) Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987.

(18) The reaction of free ester with {CD·Nuc}, which is kinetically equivalent to the process in eq 4, is considered explicitly in the Discussion.

(19) Mezei, L. M. *Practical Spreadsheet Statistics and Curve-fitting for Scientists and Engineers*; Prentice-Hall: Englewood Cliffs, NJ, 1990.

(20) The regression analysis gave: $k_u = 0.0986 \pm 0.0047\ s^{-1}$; $k_c = 0.925 \pm 0.003\ s^{-1}$; $k_N = 14.9 \pm 0.9\ M^{-1}\ s^{-1}$; $k_{cN} = 244 \pm 5\ M^{-1}\ s^{-1}$ ($r = 0.9999$). For comparison, measurements of k_{obsd} at five different $[amine]_o$, in the absence of a CD, gave $k_u = 0.0937 \pm 0.0005\ s^{-1}$ and $k_N = 16.7 \pm 0.2\ M^{-1}\ s^{-1}$ ($r = 0.9999$).

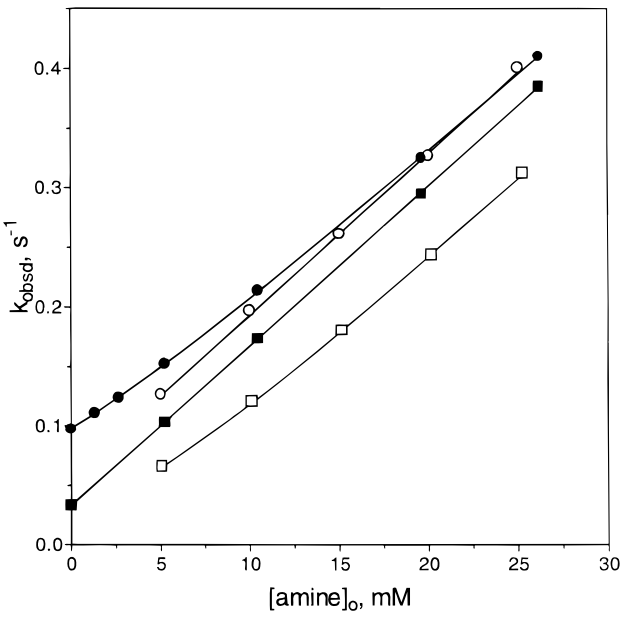


Figure 3. Rate constants for the reaction of *p*-nitrophenyl acetate with *n*-pentylamine in the absence of CD (■) and in the presence of 5.0 mM α-CD (□), 2.0 mM *β*-CD (●), and 5.0 mM *γ*-CD (○). The curves through the data for the CDs were calculated from eq 5, using fitted constants obtained from the analysis based on eq 6.

present. In the absence of CD (the lowest set of data in Figure 2), k_{obsd} increases linearly with [amine]$_o$, as expected,[21] but with added CD more complex dependence is observed because of the combined effects of two equilibria (eqs 2 and 7) and four competing kinetic processes. As [amine]$_o$ is increased, some of the free CD becomes bound to the amine, so that [CD] decreases, and the contribution from the ester cleavage by the CD (eq 2) is reduced. At the same time, the contributions from the two aminolysis pathways increase but only at high [amine]$_o$ do they dominate, as seen in Figure 2 for the set of points where [CD]$_o$ = 2.0 mM. As shown by the examples in Figure 3, an upward trend in k_{obsd} at high [amine]$_o$ is much more evident with smaller amines because these can be taken to higher [amine]$_o$ and they bind to CDs more weakly.[22]

In general, we made two sets of measurements of k_{obsd} with varying [amine]$_o$ for each combination of ester, amine, and CD (e.g., Figure 3). The first set, with no CD present, was used to find k_N accurately, and the second set, with CD present, was required to probe for k_{cN}. The two sets together were used to estimate k_{cN} from the multiple regression analysis in terms of eq 6. If the data did not give a satisfactory analysis, measurements were made at another [CD]$_o$.

Table 2 contains the values of k_N found for pNPA and pNPH reacting with six linear *n*-alkylamines, isobutylamine, isopentylamine, cyclopentylamine, cyclohexylamine, and benzylamine in the absence of CDs. For reasons of solubility, k_N for *n*-octylamine could not be obtained readily, and so we take it to be the same as for *n*-heptylamine, since chain length effects on k_N are minimal beyond C_4.[23] Table 3 presents values of k_{cN} obtained for pNPA and pNPH reacting with the amines in the presence of the four CDs, while Table 4 contains values of k_N and k_{cN} for *n*-heptylamine reacting with a series of *p*-nitrophenyl alkanoates.

Table 2. Second-Order Rate Constants (k_N) for the Reaction of Alkylamines with *p*-Nitrophenyl Acetate (pNPA) and *p*-Nitrophenyl Hexanoate (pNPH)[a]

amine	[amine]$_o$, mM	pNPA	pNPH
n-propyl	0−250	10.6 ± 0.1	4.97 ± 0.08
n-butyl	0−100	13.0 ± 0.1	6.67 ± 0.10
n-pentyl	0−25	13.4 ± 0.1	6.43 ± 0.03
n-hexyl	0−10	15.8 ± 0.3	8.46 ± 0.05
n-heptyl	0−5	16.7 ± 0.2	7.05 ± 0.10
n-octyl		16.7[b]	7.05[b]
isobutyl	0−100	7.51 ± 0.14	4.19 ± 0.04
isopentyl	0−25	14.1 ± 0.2	7.88 ± 0.10
cyclopentyl	0−70	2.73 ± 0.01	1.30 ± 0.02
cyclohexyl	0−29	1.71 ± 0.01	0.837 ± 0.016
benzyl	0−12	2.99 ± 0.05	1.21 ± 0.01

[a] Conditions as given in footnote a, Table 1. Units of k_N are M^{-1} s^{-1}. The range of amine concentration used to find k_N is given under [amine]$_o$. [b] Not easily determined because of the low solubility of the amine in water, and so the value was assumed to be the same as for *n*-heptylamine.

Tables 3 and 4 also contain other "kinetic" parameters, derived from k_N and k_{cN}, that will be used in the Discussion. First, there are third-order rate constants (k_3) for reaction of the ester, CD and amine (eq 8), where $k_3 = k_{cN}/K_S$ because of the kinetic equivalence of the processes in eqs 4 and 8. Second, from k_3 we have evaluated $k_{Nc} = k_3K_N$ for the other kinetically equivalent process in which free ester reacts with CD-bound amine (eq 9). Third, the tables include "dissociation constants", K_{TS}, which provide a measure of the strength of binding of the transition states of CD-mediated reactions to the CDs.[3] Such constants, which have been used extensively by us[3,6−8,9b,10] and others,[24] are obtained using an approach based on transition state theory.[24a] For the present purposes, K_{TS} is defined (eq 10) as the apparent dissociation constant of the transition state of the CD-mediated aminolysis (TS·CD) (eq 4, 8, or 9) into the transition state of normal aminolysis (TS) (eq 3) and the CD.

$$S + CD + Nuc \xrightarrow{k_3} \text{products} \qquad (8)$$

(21) Rate expressions for ester aminolysis often contain a term in [amine]^2, but generally only for nonaqueous solutions and when [amine] is high. In none of our experiments did we see any second order dependence on amine. Likewise, for the aminolysis of phenyl acetate by *n*-alkylamines in water, no term in [amine]^2 was detected by Bruice and co-workers: Bruice, T. C.; Donzel, A.; Huffman, R. W.; Butler, A. R. *J. Am. Chem. Soc.* **1967**, *89*, 2106.

(22) At first sight, more clear-cut aminolysis data could be obtained by carrying out experiments at a lower pH (10.6, say), where the pH-dependent background processes (eqs 1 and 2) are 10 times slower. However, at such a pH, binding of both the amine and its protonated form to the CD would complicate a full analysis.

(23) The variations of k_N for the linear *n*-alkylamines in Table 2 are not considered significant. They are attributed to the fact that some experiments were carried out in amine buffers but others employed a phosphate buffer (see Table 1 for details), where buffer catalysis (vide infra) possibly intrudes.

(24) (a) The approach was pioneered by Kurz in the context of catalysis by acids and bases: Kurz, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 987. *Acc. Chem. Res.* **1972**, *5*, 1. Some other examples of its use are in (b) Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10. (c) Leinhard, G. E. *Science* (Washington, D. C.) **1973**, *180*, 149. (d) Kraut, J. *Science* (Washington, D. C.) **1988**, *242*, 533. (e) Wolfenden, R.; Kati, W. M. *Acc. Chem. Res.* **1991**, *24*, 209. (f) Pregel, M. J.; Dunn, E. J.; Buncel, E. *J. Am. Chem. Soc.* **1991**, *113*, 3545. (g) Palmer, D. R. J.; Buncel, E.; Thatcher, G. R. J. *J. Org. Chem.* **1994**, *59*, 5286. (h) Kirby, A. *J. Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 707. (i) Davies, D. M.; Foggo, S. J.; Paradis, P. M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1597. (j) Pirrinccioiglu, N.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 37.

Table 3. Constants for the Reaction of Alkylamines with *p*-Nitrophenyl Acetate (pNPA) and *p*-Nitrophenyl Hexanoate (pNPH) in the Presence of Cyclodextrins[a]

amine	k_{cN}, M^{-1} s^{-1}	k_{cN}/k_N	k_3, M^{-2} s^{-1}	k_{Nc}, M^{-1} s^{-1}	k_{Nc}/k_N	K_{TS}, mM
(a) pNPA + α-CD (K_S = 10.5 mM)						
n-propyl	13.7 ± 0.8	1.3	1300	61	5.7	8.1
n-butyl	16.7 ± 1.2	1.3	1600	21	1.6	8.2
n-pentyl	12.2 ± 1.0	0.91	1200	3.6	0.27	12
n-hexyl	19.2 ± 3.3	1.2	1800	2.9	0.19	8.6
n-heptyl	126 ± 4	7.5	12000	5.2	0.31	1.4
n-octyl	457 ± 18	27	44000	5.8	0.35	0.38
(b) pNPA + β-CD (K_S = 7.92 mM)						
n-propyl	14.3 ± 0.8	1.4	1800	195	18	5.9
n-butyl	17.2 ± 2.0	1.3	2200	77	6.0	6.0
n-pentyl	24.7 ± 0.5	1.8	3100	36	2.7	4.3
n-hexyl	181 ± 2	11	23000	60	3.8	0.69
n-heptyl	244 ± 5	15	31000	29	1.8	0.54
n-octyl	1265 ± 4	76	160000	44	2.6	0.11
isobutyl	9.94 ± 2.0	1.3	1300	20	2.7	6.0
isopentyl	60.1 ± 2.9	4.3	7600	44	3.1	1.9
cyclopentyl	9.78 ± 0.67	3.6	1200	17	6.1	2.2
cyclohexyl	19.2 ± 2.5	11	2400	4.4	2.6	0.71
benzyl	12.9 ± 0.5	4.3	1600	24	7.9	1.8
(c) pNPA + hp-β-CD (K_S = 8.20 mM)						
n-propyl	5.13 ± 0.78	0.48	630	88	8.3	17
n-butyl	8.55 ± 1.08	0.66	1040	44	3.4	13
n-pentyl	6.67 ± 1.14	0.50	810	11	0.83	17
n-hexyl	57.2 ± 5.1	3.6	7000	34	2.1	2.3
n-heptyl	59.1 ± 6.4	3.5	7200	9.5	0.57	2.3
n-octyl	185 ± 4	11	23000	12	0.70	0.74
cyclopentyl	4.82 ± 0.30	1.8	590	9.5	3.5	4.6
cyclohexyl	*b*					
(d) pNPA + γ-CD (K_S = 35.6 mM)						
n-propyl	33.9 ± 1.8	3.2	950	142	13	11
n-butyl	24.9 ± 2.1	1.9	700	46	3.5	19
n-pentyl	51.2 ± 2.3	3.8	1400	28	2.1	9.3
n-hexyl	263 ± 7	17	7400	69	4.3	2.1
n-heptyl	736 ± 24	44	21000	58	3.5	0.81
n-octyl	2960 ± 20	180	83000	93	5.6	0.20
(e) pNPH + α-CD (K_S = 2.90 mM)						
n-propyl	4.13 ± 0.26	0.83	1400	66	13	3.5
n-butyl	5.47 ± 0.38	0.82	1900	25	3.8	3.5
n-pentyl	5.02 ± 0.46	0.78	1700	5.3	0.83	3.7
n-hexyl	4.45 ± 0.99	0.53	1500	2.5	0.29	5.5
n-heptyl	12.8 ± 0.5	1.8	4400	1.9	0.27	1.6
n-octyl	114 ± 26	16.2	39000	5.3	0.75	0.18
(f) pNPH + β-CD (K_S = 1.60 mM)						
n-propyl	1.58 ± 0.19	0.32	990	110	21	5.0
n-butyl	3.84 ± 0.22	0.58	2400	85	13	2.8
n-pentyl	6.89 ± 0.12	1.1	4300	49	7.6	1.5
n-hexyl	43.5 ± 2.1	5.1	27000	71	8.4	0.31
n-heptyl	63.9 ± 2.0	9.1	40000	38	5.4	0.18
n-octyl	270 ± 17	38	170000	47	6.6	0.042
isobutyl	1.72 ± 0.25	0.41	1100	17	4.2	3.9
isopentyl	13.6 ± 0.4	1.7	8500	49	6.3	0.93
cyclopentyl	3.01 ± 0.06	2.3	1900	25	20	0.69
cyclohexyl	7.78 ± 0.17	9.3	4900	9.0	11	0.17
benzyl	3.71 ± 0.05	3.1	2300	34	28	0.52
(g) pNPH + hp-β-CD (K_S = 1.59 mM)						
n-propyl	0.662 ± 0.336	0.13	420	59	12	12
n-butyl	0.512 ± 0.194	0.077	320	14	2.0	21
n-pentyl	2.24 ± 0.11	0.35	1400	19	3.0	4.6
n-hexyl	9.32 ± 0.45	1.1	5900	28	3.3	1.4
n-heptyl	12.1 ± 1.0	1.7	7600	10	1.4	0.93
n-octyl	23.1 ± 2.6	3.3	14500	7.5	1.1	0.49
cyclopentyl	0.709 ± 0.039	0.55	450	7.2	5.5	2.9
cyclohexyl	*b*					
(h) pNPH + γ-CD (K_S = 10.7 mM)						
n-propyl	6.63 ± 0.8	1.3	620	92	19	8.0
n-butyl	4.85 ± 2.0	0.73	450	30	4.5	15
n-pentyl	12.3 ± 0.5	1.9	1200	22	3.5	5.6
n-hexyl	22.7 ± 0.7	2.7	2100	20	2.3	4.0
n-heptyl	179 ± 5	25	17000	48	6.7	0.42
n-octyl	688 ± 4	98	64000	72	10	0.11

[a] See footnote a, Table 1. The values of K_S are taken from earlier work.[7,8] [b] For the reactions of pNPA and pNPH with cyclohexylamine in the presence of hp-β-CD the data analysis was unacceptable (see Experimental Section).

Table 4. Constants for the Reaction of *n*-Heptylamine with *p*-Nitrophenyl Alkanoates in the Presence of Cyclodextrins[a]

ester	K_S, mM	k_{cN}, M^{-1} s^{-1}	k_{cN}/k_N	k_3, M^{-2} s^{-1}	k_{Nc}, M^{-1} s^{-1}	k_{Nc}/k_N	K_{TS}, mM
(a) α-Cyclodextrin							
acetate	10.5	126 ± 5	7.5	12000	5.2	0.31	1.4
propanoate	7.4	51.9 ± 3	4.3	7000	3.0	0.25	1.7
butanoate	5.0	21.0 ± 8.3	2.8	4200	1.8	0.24	1.8
pentanoate	3.4	12.1 ± 2.5	1.6	3600	1.5	0.20	2.2
hexanoate	2.9	12.8 ± 2.0	1.8	4400	1.9	0.27	1.6
(b) β-Cyclodextrin							
acetate	7.9	244 ± 5	15	31000	29	1.8	0.54
propionate	5.2	105 ± 3	8.8	20000	19	1.6	0.59
butanoate	2.7	60.7 ± 8.3	8.2	22000	22	2.9	0.33
pentanoate	2.0	54.0 ± 2.5	6.9	27000	26	3.3	0.29
hexanoate	1.6	63.9 ± 2.0	9.1	40000	38	5.4	0.18
(c) Hydroxypropyl-β-cyclodextrin							
acetate	8.2	59.1 ± 6.4	3.5	7200	9.5	0.57	2.3
propanoate	5.1	16.0 ± 2.8	1.3	3200	4.1	0.35	3.8
butanoate	2.7	8.36 ± 0.57	1.1	3100	4.1	0.55	2.4
pentanoate	1.9	14.0 ± 0.9	1.8	7200	9.7	1.3	1.1
hexanoate	1.6	12.1 ± 1.0	1.7	7600	10	1.4	0.93
(d) γ-Cyclodextrin							
acetate	36	736 ± 24	44	20000	58	3.5	0.82
propanoate	32	749 ± 8	63	23000	67	5.5	0.51
butanoate	15	264 ± 2	36	18000	50	6.8	0.42
pentanoate	15	282 ± 2	36	19000	53	6.9	0.41
hexanoate	11	179 ± 5	25	16000	46	6.6	0.43
heptanoate	12	200 ± 1	28	17000	47	6.7	0.42

[a] At 25 °C, in a 0.2 M phosphate buffer of pH 11.60. The values of K_S are taken from earlier studies.[7,8] For reaction of the esters with *n*-heptylamine in the absence of CDs the rate constants (k_N, in M^{-1} s^{-1}) are: acetate, 16.7 ± 0.2; propanoate, 12.0 ± 0.1; butanoate, 7.41 ± 0.04; pentanoate, 7.78 ± 0.06, hexanoate, 7.05 ± 0.10; heptanoate, 7.05 (assumed to be the same as the hexanoate).

$$S + CD{\cdot}Nuc \xrightarrow{k_{Nc}} \text{products} \quad (9)$$

$$K_{TS} = [TS][CD]/[TS{\cdot}CD] = k_N K_S/k_{cN} = k_N/k_3 = k_N K_N/k_{Nc} \quad (10)$$

Discussion

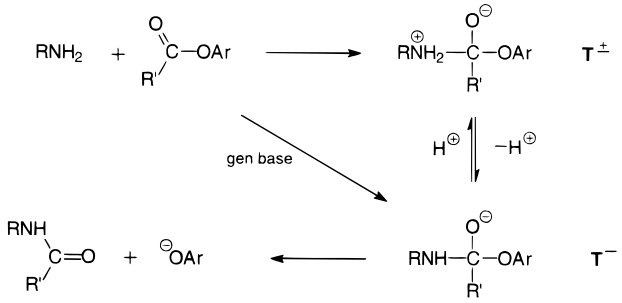
Overview. The aminolysis of aryl esters[25] takes place most simply by formation of a zwitterionic intermediate $\mathbf{T}^{\pm}$ which undergoes fast deprotonation at high pH, followed by the loss of aryloxide ion from its anion, $\mathbf{T}^{-}$ (Scheme 1). In some instances $\mathbf{T}^{-}$ is formed directly from the reactants by general base assistance from hydroxide ion, a second molecule of amine, or the buffer base.[26] Regardless of the finer details of the mechanism, the rate-limiting transition state should resemble $\mathbf{T}^{\pm}$ or $\mathbf{T}^{-}$ and, by inference from Hammond's Postulate,[27] factors that can stabilize these intermediates are expected to lower the overall activation barrier.

(25) (a) Background references on ester aminolysis can be found in: Adalsteinsson, H.; Bruice, T. C.; *J. Am. Chem. Soc.* **1998**, *120*, 3440, and Koh, H. J.; Shin, C. H.; Lee, H. W.; Lee, I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1329. (b) DeTar, D. F.; Delahunty, C. *J. Am. Chem. Soc.* **1983**, *105*, 2734. (c) Henge, A. C.; Hess, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 11256.

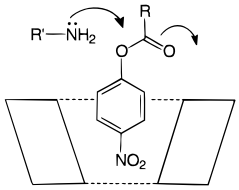
(26) Because of general base catalysis, pseudo-first-order rate constants for the aminolysis of esters may contain terms in $[amine]^2$, $[amine][OH^-]$, and [amine][buffer], depending on the reactants and the solvent.[25] However, as remarked above,[21] our plots of k_{obsd} against $[amine]_o$ in the absence of a CD were all strictly linear.

(27) (a) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334. (b) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: Oxford, 1985; pp 261−263.

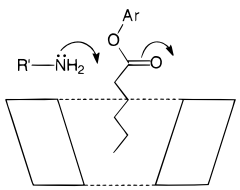
Scheme 1



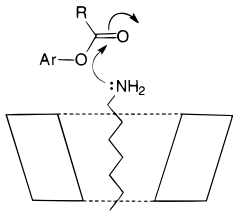
In a CD-mediated aminolysis, stabilization of the intermediates $\mathbf{T}^{\pm}$ and $\mathbf{T}^{-}$, and the transition states adjacent to them, may occur by binding of the CD to one of three loci: the alkyl portion (R) of the alkylamino group, the alkyl group (R′) of the proacyl group, and the aryl group (Ar) of the nucleofuge (Scheme 1). A preference for binding one of these three groups will depend on their nature, but in the absence of any unusual interactions it should follow established trends. If both R and R′ are quite small, the CD is expected to bind preferentially to the aryl group (Ar = *p*-nitrophenyl). For a long ester, and short amine, the preference may be for inclusion of R′ of the proacyl group. However, for reaction by a long amine with a short ester the transition state may be bound by the alkylamino group, R. Therefore, at the outset we envisage three main possibilities for aryl ester aminolysis mediated by a cyclodextrin: (i) reaction of the aryl-bound ester with amine external to the CD cavity (**3**); (ii) reaction of the acyl-bound ester with the amine outside the CD cavity (**4**); (iii) reaction between CD-bound amine with the free ester (**5**).



3

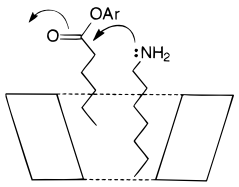


4

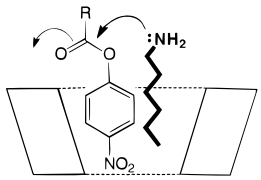


5

If the alkylamine and the alkanoate ester both have fairly long alkyl groups then a competition between binding of $R-NH_2$ and R′-CO is set up, and it is not clear what the preferred mode of transition state binding might be (**4** or **5**). Moreover, with γ-CD, and maybe even with β-CD, there is the possibility of partial inclusion of both of the alkyl groups, R and R′ (**6**). Likewise, if the CD cavity is large enough to permit it, there might be some inclusion of the aryl group of the ester and the alkyl group of the amine (**7**).



6



7

Reactions proceeding through the CD-bound termolecular transition states **3** to **7** are kinetically equivalent and distinction between them is possible only by analyzing how kinetic parameters (e.g., k_{cN}/k_N, k_3, and K_{TS})[3,7,8] vary with the structures of the ester, the amine, and the CD. If the reaction occurs with aryl group inclusion, **3**, the parameters should be insensitive to $R-NH_2$ and R′−CO, while for reaction through **4** they should vary with the ester acyl group R′CO, and for transition state **5** they should vary with the alkylamino group, RNH_2. Likewise, for the transition state **6**, the parameters should show sensitivity to the alkyl groups of both the amine and the ester, but if it involves **7** then there should be sensitivity to Ar and RNH_2, but not to R′CO.

Even a cursory viewing of Tables 3 and 4 will note that the various kinetic parameters for CD-mediated aminolysis vary substantially with the amine, the ester and the CD. For instance, the third-order rate constants k_3 (eq 8) vary from 590 to 160000 M^{-2} s^{-1} for pNPA, and from 320 to 170000 M^{-2} s^{-1} for pNPH (Table 3). Moreover, there are specific trends in the parameters as the chain lengths of R and R′ are increased, and there are differences between the effects of the four CDs.

Reactivity Ratios (k_{cN}/k_N and k_{Nc}/k_N). The ratio k_{cN}/k_N is a measure of the relative reactivities of the CD-bound and free forms of the ester toward the nucleophile, assuming the CD-mediated reaction is that in eq 4, whereas k_{Nc}/k_N measures the relative reactivities of the CD-bound and free amine toward unbound ester for reaction as in eq 9. Note also, that by virtue of the form of K_{TS} in eq 10, the logarithms of the reactivity ratios reflect differences between transition state binding and substrate (ester or amine) binding, as shown in eq 11.

$$\log(k_{cN}/k_N) = pK_{TS} - pK_S;\ \log(k_{Nc}/k_N) = pK_{TS} - pK_N \quad (11)$$

For the reaction of nonbinding nucleophiles with *p*-nitrophenyl alkanoate esters values of k_{cN}/k_N are small and close to one (0.14 to 1.7),[10] and for the anions of TFE and 2-ME there are biphasic variations in these ratios (and other parameters) with ester chain length that indicate a switch from reaction mode **1** for the short esters to **2** for the longer esters.[10b] The present study shows that for the aminolysis of the same esters in the presence of CDs the corresponding ratios vary much more widely, from 0.08 to 180 (Table 3).

The cleavage of pNPA by *n*-alkylamines exhibits k_{cN}/k_N ratios that are small, not far from one, and nearly constant for short amines (3, 4, 5, or 6 carbons), after which they increase dramatically (Figure 4), up to 180 for catalysis by γ-CD (Table 3). Similar trends are observed for the aminolysis of pNPH, although the ratios are generally smaller (Table 3). This largely biphasic behavior, which is seen for all four CDs (Figure 4), is evidence that short alkylamines react with the CD-bound

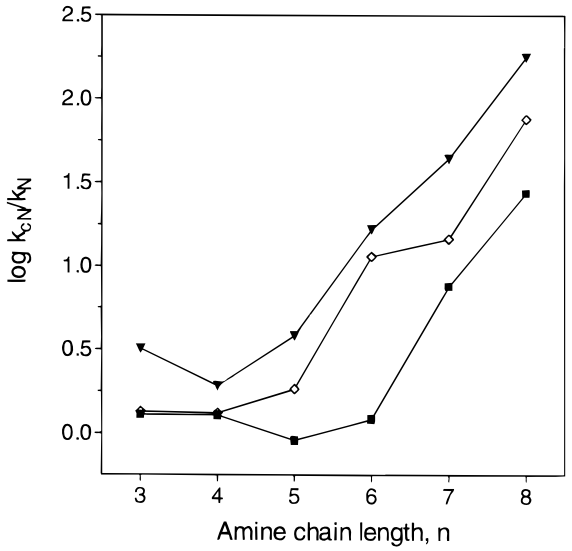


Figure 4. Dependence of reactivity ratios k_{cN}/k_N (Table 3) on amine chain length for the CD-mediated reaction of pNPA with *n*-alkylamines. The symbols are for the CDs as follows: ■, α-CD; ◇, *β*-CD; ▼, *γ*-CD.

ester (**3**) but longer amines are bound to the CD and they react with free ester (**5**). Alternatively, if the CD-mediated reaction entails reaction of free ester with CD-bound amine (eq 9) the relevant ratios, k_{Nc}/k_N, show exactly opposite dependencies on amine chain length as they decrease for the short amines and they are essentially constant for the longer amines. This behavior is also consistent with a change in the mode of reaction from **3** to **5**, as the amine chain becomes longer. Note that in most cases where reaction is mediated by *β*-CD and *γ*-CD both reactivity ratios are greater than one, which means that the aminolysis is truly catalyzed in those cases, regardless of the precise mechanism.

The CD-mediated reaction of *n*-heptylamine with *p*-nitrophenyl alkanoates shows ratios of k_{cN}/k_N that vary only marginally with acyl chain length but substantially with the CD (Table 4). This insensitivity to ester chain length is evidence against reaction by acyl group binding (**4**), but it does not preclude some participation of the aryl group and it is consistent with alkylamino group binding (**5**), as suggested for longer amines, in the previous paragraph. Most noteworthy, the ratios k_{cN}/k_N for any given ester increase in the order: *γ*-CD > *β*-CD > α-CD ≥ hp-*β*-CD, with those for *γ*-CD being 10 to 30 times greater than those for hp-*β*-CD. Also, the ratios for *γ*-CD are all much greater than one (25 to 63), implying substantial catalysis if the reaction takes place between bound ester and free amine (eq 4, and **3**).

For the reaction of *n*-heptylamine with *p*-nitrophenyl alkanoates in the presence of α-CD, the ratios k_{Nc}/k_N fall in the narrow range 0.20−0.31 (Table 4) and are insensitive to the ester chain length. With *γ*-CD, values of k_{Nc}/k_N are 10 to 30 times larger and remarkably constant for the C_4 to C_7 esters (6.8, 6.9, 6.6, 6.7). These results for α-CD and *γ*-CD are compatible with transition state binding of the alkylamino group (**5**), and not of the acyl group (**4**), but there must be some additional interaction to account for the 10- to 30-fold greater reactivity observed with *γ*-CD. Also with respect to the results for *γ*-CD in Table 4, note that both k_{cN}/k_N and k_{Nc}/k_N are greater than one (25−60 and 3.5−6.9, respectively), meaning that aminolysis of the esters by *n*-heptylamine is definitely catalyzed by *γ*-CD.

The ratios k_{Nc}/k_N for *β*-CD and hp-*β*-CD are intermediate between those for α-CD and *γ*-CD (Table 4), as expected if the differences are related to cavity size. Conceivably, α-CD holds the alkylamino group rigidly so that the aminolysis is impaired ($k_{Nc}/k_N < 1$), but the much wider cavity of *γ*-CD[11] is large enough that it can partially accommodate the aryl group of the ester moiety, as well as the alkylamino group (**7**), or at least interact favorably with it. In this regard, it is important to note that by themselves *p*-nitrophenyl alkanoates bind to *γ*-CD by aryl group inclusion,[8b] and not by acyl group inclusion, which is the case for the longer (>C_4) esters binding to the other CDs.[7,8]

Values of k_{Nc}/k_N for reaction of the esters with *n*-heptylamine in the presence of *β*-CD and hp-*β*-CD are not constant, and they increase about 3-fold from the acetate to the hexanoate (Table 4). These increases conceivably denote partial inclusion of the longer ester chains, as well as of the amine chain (**6**). Comparing hp-*β*-CD to *β*-CD, both reactivity ratios are smaller and closer to one for the alkylated CD derivative, perhaps because its hydroxypropyl groups on the primary side to the cavity[1c] form an intrusive floor[28] that reduces its ability to bind to the transition state for aminolysis, whatever the moiety included in the cavity.

Third-Order Reactivity (k_3). A more unbiased view of CD-mediated aminolysis is obtained by looking at the rate constants for the third-order process in eq 8. These constants (k_3) are a measure of the Gibbs energy of the transition state composed of {amine + ester + CD}, relative to the separate reactants in the initial state, without any assumptions being made about the reaction mechanism. Variations of k_3 with the structures of the reactants may provide insight into the structure(s) of the termolecular transition states.[3]

For the reaction of various amines with pNPA and pNPH, mediated by the four CDs, k_3 varies over a 270-fold range for pNPA and over a 530-fold range for pNPH (Table 3 and Figure 5). Less than a factor of 10 of these large ranges are due to differences in amine/ester reactivity (see k_N values, Table 2), and so they must be due to variations in the transition state stabilization afforded by the different CDs.

As seen in Figure 5, the variations of k_3 on amine chain length are biphasic, being comparatively invariant for short amines and increasing steeply for the longer ones. With α-CD the point of inflection for both esters is at C_6 while for the wider *γ*-CD it is at C_4. The picture is less consistent for *β*-CD and hp-*β*-CD, with the breakpoint being at C_4 (pNPH/hp-*β*-CD), or C_5 (pNPA/*β*-CD and pNPA/hp-*β*-CD), or barely discernible (pNPH/*β*-CD). Nevertheless, Figure 5, like Figure 4, provides strong evidence of a general change in the mode of transition state binding from aryl group inclusion (**3**) for short amines to alkylamino group inclusion for long amines (**5**), and the possibility of reaction with alkylamino group inclusion and some acyl group or aryl group binding (**6** or **7**).

(28) The cleavage of nitrophenyl alkanoate esters by hp-*β*-CD is less efficient than that by *β*-CD.[8a] Other functionalities on the primary side of *β*-CD that provide an intrusive floor to the cavity generally lead to slower ester cleavage. For examples, see: Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762. Fujita, K.; Shinoda, A.; Imoto, T. *J. Am. Chem. Soc.* **1980**, *102*, 1161.

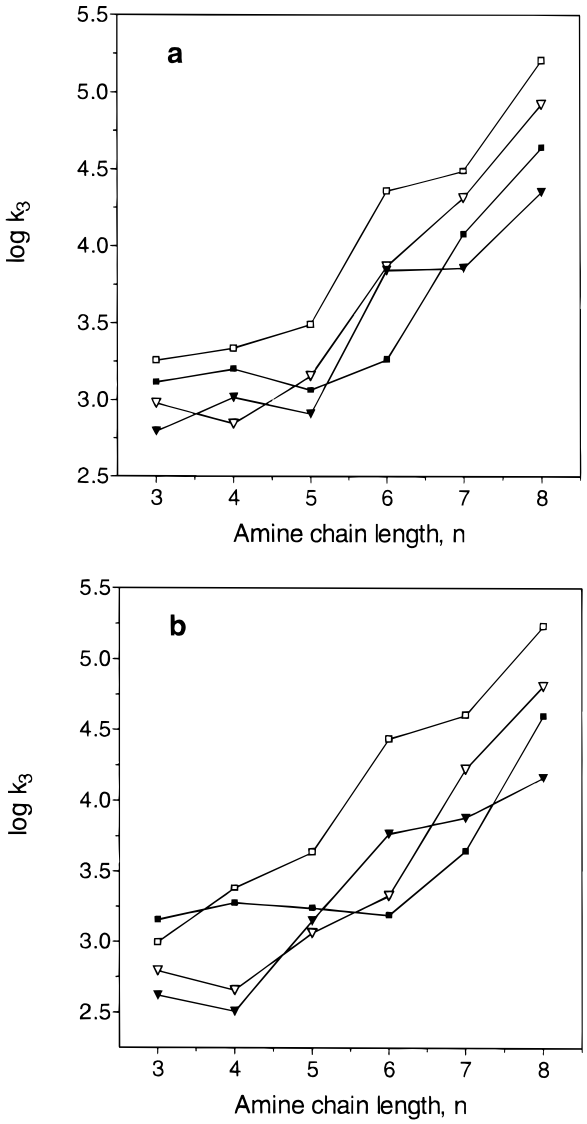


Figure 5. Chain length dependence of the third-order rate constants (k_3, Table 3) for the reaction of ester (pNPA or pNPH) + *n*-alkylamine + CD. (a) Ester = pNPA; (b) ester = pNPH. In both cases the symbols for the CDs as follows: ■, α-CD; □, *β*-CD; ▼, hp-*β*-CD; ▽, *γ*-CD.

By contrast, values of k_3 for the reaction of *p*-nitrophenyl alkanoates with *n*-heptylamine show little dependence on the ester chain (Table 4). Broadly speaking, for a given ester the reactivity varies as: *β*-CD > *γ*-CD > α-CD > hp-*β*-CD, which reflects the relative amounts of transition state stabilization[3] afforded by the CDs (see below). Therefore, there must be stabilizing factors with *β*-CD and *γ*-CD which are reduced or absent in the case of α-CD and hp-*β*-CD. For α-CD, k_3 decreases from the C_2 to C_4 esters and then remains constant, parallel to k_N for reaction in the absence of the CD (Table 2), and consistent with alkylamino group inclusion and no acyl group inclusion in the transition state (i.e., **5**). With *β*-CD and hp-*β*-CD, k_3 values decrease somewhat and then increase, suggesting at least two factors are involved and that there is switch between their dominance. Conceivably, for the long esters there is partial acyl chain inclusion, as well as of the alkylamino group (**6**). Most remarkably, the six values of k_3 for catalysis by *γ*-CD are almost constant (17000 to 23000 M^{-2} s^{-1}), consistent with a transition state involving alkylamino inclusion (**5**) or a combination of alkylamino inclusion and aryl inclusion (**7**), bearing in mind that *p*-nitrophenyl alkanoates bind to *γ*-CD by aryl group inclusion.[8b]

Transition State Stabilization (pK_{TS}). In our view,[3] the best parameter for probing transition state binding is K_{TS}, the apparent dissociation constant of the CD-containing transition state (eq 10), and $pK_{TS} = -\log K_{TS}$. Since pK_{TS} is a measure of the stabilization of a transition state by the CD, variations of it with structure can provide information about transition state binding.[3,24] For the present results, the variations of pK_{TS} with the amine, the ester, and the CD are shown in Figures 6, 7, and 8.

The dependence of pK_{TS} on the binding ability of the amine (pK_N) for aminolysis of pNPA and pNPH in the presence of α-CD is distinctly biphasic (Figure 6a). For short amines (C_3 to C_6), pK_{TS} is insensitive to pK_N, as expected for aryl inclusion in the transition state (**3**) but note that pK_{TS} is decidedly larger for pNPH than for pNPA, implying that there is some additional stabilization due to the longer acyl chain of pNPH. For amines beyond C_6, the values of pK_{TS} rise steeply with pK_N, with slopes near 1 (1.3 and 1.4) that are perfectly in accord with the reaction taking place between CD-bound amine and free ester (**5**). Furthermore, for the long amines the values of pK_{TS} for pNPA and pNPH are essentially the same, also consistent with a transition state that has the ester acyl chain outside the α-CD cavity, as in **5**.

Figures 6b and 6c show plots of pK_{TS} vs pK_N for the aminolysis of pNPA and pNPH in the presence of *β*-CD and hp-*β*-CD. With hp-*β*-CD the dependence is also essentially biphasic, in keeping with a switch from mode 3 to mode 5, the breakpoints being at C_4 for pNPA and at C_3 for pNPH. Likewise, for pNPA reacting in the presence of *β*-CD, there is a change in behavior at C_3 or C_4, but for pNPH there is no clear inflection as pK_{TS} rises consistently with pK_N (Figure 6b). The values of pK_{TS} for pNPA and pNPH reacting with *n*-propylamine are essentially equal, as expected if both react with aryl group inclusion (**3**). For amines longer than *n*-propyl, pK_{TS} for pNPH increases with pK_N linearly ($r = 0.992$) and with a slope of 0.80, implying that the ester reacts with inclusion of the alkylamino group, as in **5** (or **6**). However, since for both *β*-CD and hp-*β*-CD, the pK_{TS} values are larger for pNPH than for pNPA there appears to be additional stabilization due to the longer acyl chain of pNPH, possibly due to partial acyl inclusion, as in **6**.

As shown in Figure 6d, for catalysis by *γ*-CD, there is little difference between the values of pK_{TS} for the aminolysis of pNPA and pNPH, suggesting that the disposition of the two esters in their transition states are virtually identical. Both esters exhibit a similar biphasic variation of pK_{TS} with pK_N, with little change for the C_3 and C_4 amines and then a dramatic increase. For the two shortest amines, the reaction probably occurs between aryl-bound ester and free amine (**3**), as for the three other CDs (see above). From the C_4 amine onward, pK_{TS} vs pK_N has slopes of 1.1 and 1.2, which are entirely consistent with alkylamino group binding in the transition state, as in **5** or **7** (discussed below).

To probe further the transition state of CD-mediated aminolysis, we consider how pK_{TS} varies with the chain lengths of the esters reacting with *n*-heptylamine in the presence of α-CD, *β*-CD, and *γ*-CD (Figure 7). In the case of α-CD, the values are low and they hardly vary with the ester, as expected if there is transition state binding

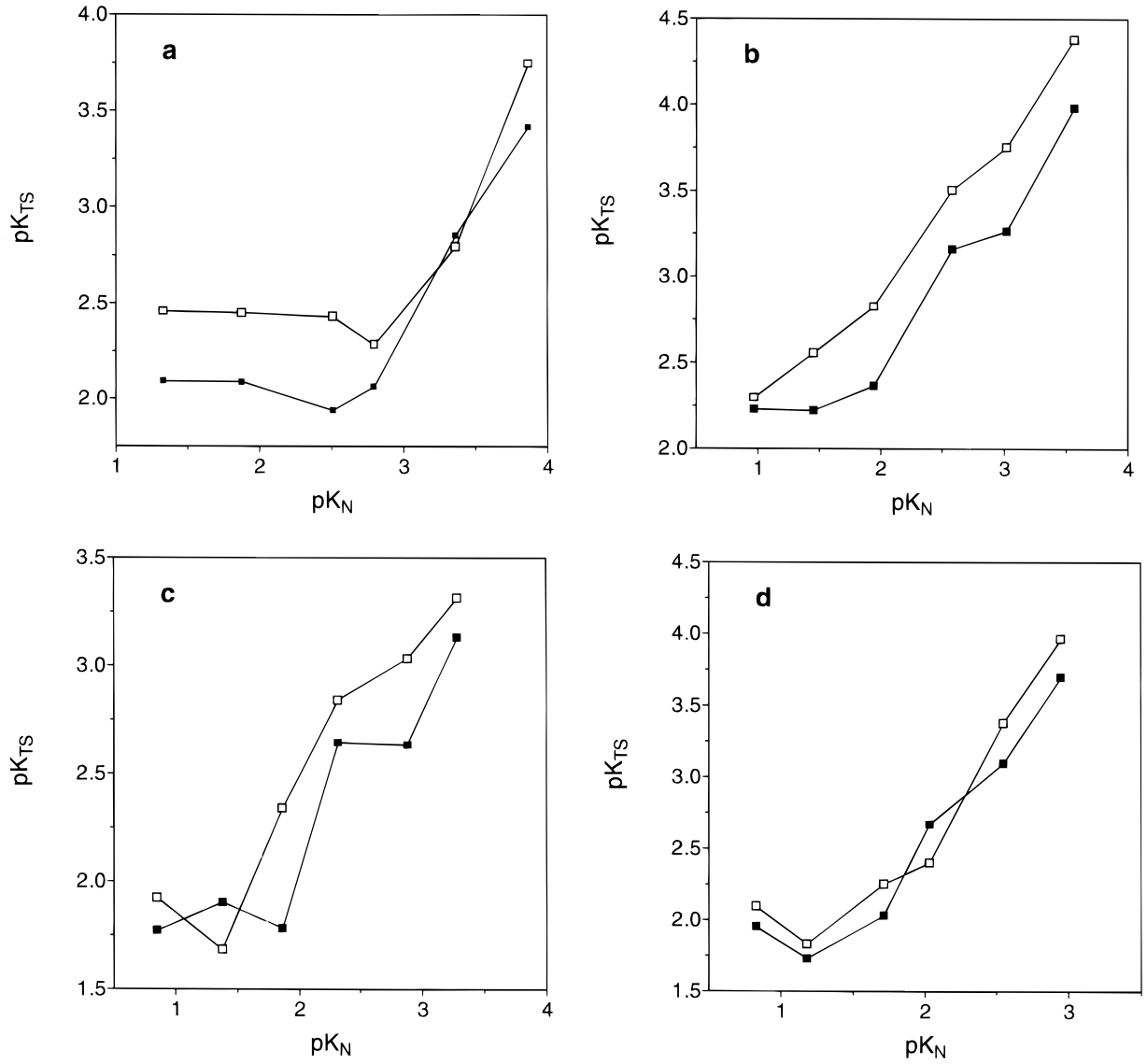


Figure 6. Correlation of transition state stabilization (pK_{TS}) with the strength of amine binding (pK_N) for the CD-mediated reaction of pNPA (■) and pNPH (□) with *n*-alkylamines: (a) α-CD; (b) *β*-CD; (c) hp-*β*-CD; (d) *γ*-CD.

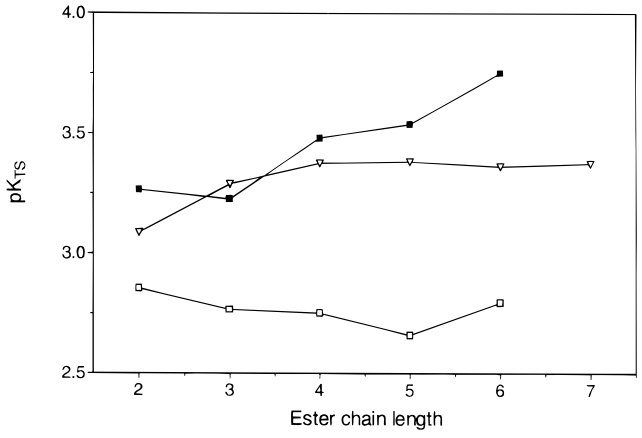


Figure 7. Dependence of transition state stabilization (pK_{TS}) on ester chain length for the CD-mediated reaction of *n*-heptylamine with *p*-nitrophenyl alkanoates (acetate to heptanoate). The symbols are: □, α-CD; ■, *β*-CD; ▽, *γ*-CD.

of the *n*-heptylamino group but not of the acyl group of the ester (**5**). For this reaction pathway (eq 9), $k_{Nc}/k_N =$ 0.2−0.3 (Table 4), implying that *n*-heptylamine bound to α-CD is 3−5 times less reactive than the free amine.

For reaction in the presence of *γ*-CD, pK_{TS} values show little variation with ester chain length, and they are much greater than those for α-CD (Figure 7) because the reaction is definitely catalyzed by *γ*-CD: both k_{cN}/k_N and $k_{Nc}/k_N > 1$ (Table 4). This behavior is consistent with transition state binding of the *n*-heptylamino group (**5**), but the lower barrier with *γ*-CD is not simply due to binding of this group because *n*-heptylamine binds more weakly to *γ*-CD than to α-CD (Table 1). Conceivably, there is partial inclusion of the *p*-nitrophenyl group of the ester (**7**) or some favorable interaction between it and the rim of the *γ*-CD cavity.

In contrast to those for α-CD and *γ*-CD, pK_{TS} values for *β*-CD increase with ester chain length (Figure 7), as do those for hp-*β*-CD. If pK_{TS} is plotted against pK_S for ester binding, the overall slopes are ∼0.7 for both CDs, implying appreciable sensitivity to ester structure. Furthermore, from the C_3 to C_6 esters the slopes of pK_{TS} against pK_S are essentially 1 (0.95 for *β*-CD; 1.27 for hp-*β*-CD), indicating that the transition state binding is as

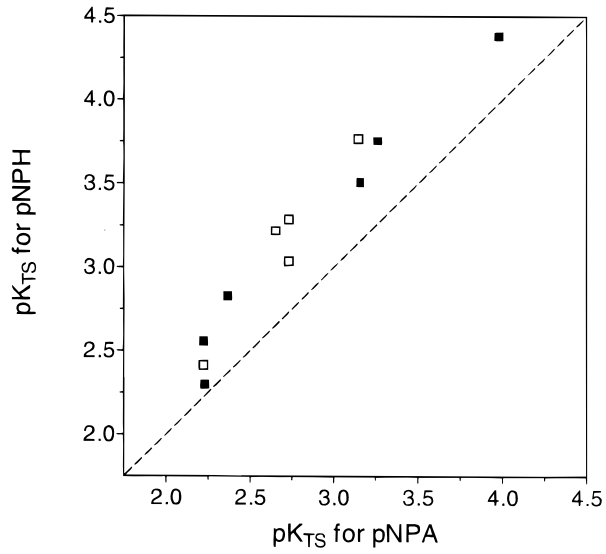


Figure 8. Comparison of transition state stabilization (pK_{TS}) by β-CD for the reactions of pNPH and pNPA with alkylamines: linear amines, ■; branched and cyclic amines, □. For almost every amine the transition state stabilization for pNPH is greater than that for pNPA.

sensitive as substrate binding to the structure of the esters, as well as being very sensitive to the amine structure (Table 3 and Figure 6b). Thus, it seems justifiable to suggest that with β-CD and hp-β-CD the aminolysis transition state is stabilized by some acyl group binding as well as by alkylamino group binding (**6**).

Branched and Cyclic Amines. Up to this point we have said nothing about the nonlinear amines: isobutyl-, isopentyl-, cyclopentyl-, cyclohexyl-, and benzylamine, aside from citing their K_N values (Table 1). As anticipated, these nucleophiles are less reactive than *n*-alkylamines toward pNPA and pNPH for steric reasons[25b] (k_N, Table 2), except for isopentylamine where the branching is far enough from the nitrogen that it reacts as fast as *n*-pentylamine. Also, as expected, the branched and cyclic amines react about twice as rapidly with pNPA as with pNPH.

The effects of β-CD on the aminolysis of pNPA and pNPH by the nonlinear amines are comparable to those for the *n*-alkylamines, as judged by the ratios k_{cN}/k_N and k_{Nc}/k_N (Table 3), which are greater than one in almost all cases, meaning that the reactions are catalyzed. Correspondingly, the nonlinear and linear amines show similar transition state binding (pK_{TS}) in relation to amine binding (pK_N), but there are minor differences. For reaction with pNPA, the two branched amines (and cyclohexylamine) have very similar parameters to the linear amines, but cyclopentylamine and benzylamine bind more strongly in the transition state. For reaction with pNPH, all three cyclic amines show superior transition state binding whereas the two branched amines bind less well in the transition state, compared to the linear amines. These differences presumably reflect the bulkiness of the amine nucleophile and how it influences the stability of the transition state structure.

A more important point is that the nonlinear amines, as well as the *n*-alkylamines, show stronger transition state binding for reaction with pNPH than with pNPA. This point is emphasized by Figure 8 which shows the values of pK_{TS} for pNPH plotted against those for pNPA, for aminolysis of the esters by all 11 amines in the presence of β-CD. The two sets of data correlate quite well, but in almost all cases pK_{TS} for pNPH is larger, and by a fairly constant amount, implying that there is an additional stabilizing interaction in the transition state due to the longer hexanoyl acyl chain of pNPH. Thus, Figure 8 provides additional support for the idea that CD-catalyzed reaction of longer esters and larger amines takes place with some inclusion of the ester acyl chain (**6**).

Conclusions

Detailed kinetic studies have shown that the aminolysis of *p*-nitrophenyl alkanoate esters by primary alkylamines is mediated by cyclodextrins and in several cases it is catalyzed by them. From the variations of kinetic parameters with structure it is proposed that at least two and possibly four different modes of transition state binding are operative: structures **3** and **5**, and possibly **6** and **7**. The principal conclusions are as follows:(i) the reaction of short alkanoate esters with short amines ($<C_6$) occurs by the attack of free amine on ester bound to the CD by its aryloxy group (**3**); (ii) for longer amines, the reaction is between free ester and CD-bound amine (**5**); (iii) the reaction of long esters with long amines is catalyzed by β-CD (and to a lesser extent by hp-β-CD) and it may involve by partial inclusion of the alkyl moieties of both reactants (**6**); (iv) γ-CD catalyzes aminolysis and its larger cavity of appears to allow the partial inclusion of the aryloxy group of the ester as well as the alkyl group of the amine in the transition state (**7**); (v) for none of the ester/amine/CD systems studied did reaction between acyl-bound ester and free amine (**4**) appear to be important; (vi) for any given ester, the catalysis is largest for long amines and the larger CDs. Finally, we point out that in a companion study of the aminolysis of naphthyl acetates we recently found appreciable catalysis by β-CD.[29]

Experimental Section

Materials. The amines, 1-anilino-8-naphthalenesulfonic acid (ANS), α-CD, β-CD, phenolphthalein, and most other chemicals were purchased as the best grades available from the Aldrich Chemical Co., whereas γ-CD and "hydroxypropyl-β-cyclodextrin" (hp-β-CD) were obtained from Wacker Chemie (Munich, Germany). As in earlier studies,[8,14] the hp-β-CD had an average molecular weight of 1500, corresponding to the alkylation of about six of the seven primary hydroxy groups of β-CD by 2-hydroxypropyl groups,[1c,28] and this formulation was confirmed by electrospray mass spectroscopy. Most of the esters were obtained from the Sigma Chemical Company except for *p*-nitrophenyl heptanoate which had been synthesized previously.[8a] Aqueous buffers were made up from the best grades of the buffer reagents available and with water, doubly distilled from glass.

Kinetic Experiments. These were carried out much the same way as in previous work on ester cleavage.[8,10] Equal volumes of the amine dissolved in a basic aqueous buffer were mixed (1:1) with an aqueous solution of the ester (10−100 μM, depending on solubility) and reacted in a stopped-flow spectrophotometer. The concentrations of all species after mixing were half of those initially present in the individual syringes. For the experiments in the presence of a CD, one syringe contained the amine in buffer, while the other syringe contained an aqueous solution of the ester and the CD (which aids

(29) Tee, O. S.; Boyd, M. J. *Can. J. Chem.* **1999**, *77*, 950.

in solubilization of the esters). The solutions containing amine were all set to pH 11.60 in a buffer. For the less soluble amines (*n*-hexyl, *n*-heptyl, *n*-octyl, isobutyl, isopentyl, and benzyl) the buffer was 0.4 M phosphate; for the remaining amines the buffer was made using the amine itself. The amine concentrations used were varied with the amine solubility, with five to seven different $[amine]_o$ ranging from 0 to 4.00 mM (for *n*-octylamine) to 0−250 mM (for *n*-propylamine).

The kinetics of cleavage of the nitrophenyl esters were followed by monitoring the first order appearance of *p*-nitrophenoxide ion at 405 nm, using an Applied Photophysics SX17MV Stopped-flow Spectrophotometer, with the temperature of the cell kept at 25.0 ± 0.1 °C. Normally, 5 to 10 good absorbance traces were collected and averaged before estimation of k_{obsd} by nonlinear least-squares fitting of an exponential growth curve to the data (400 points). With the least soluble esters, present at very low concentration, more traces were averaged if necessary.

Data Analysis. Values of k_{obsd} obtained at different levels of $[CD]_o$ and $[amine]_o$ were analyzed in terms of eq 6 (Nuc = amine) by multiple linear regression analysis of the dependence of k_{obsd}/f_S on [CD], [amine], and [CD][amine] using Lotus 123 spreadsheet software.[19] From this analysis the rate constant k_{cN} was obtained from the fitted coefficient for the term in [CD][amine], which equals k_{cN}/K_S (= k_3). Although a value of k_N can be obtained from the same analysis, it was more accurately determined from measurements made in the absence of CD when $k_{obsd} = k_u + k_N[amine]_o$.

Analysis in terms of eq 6 requires values of [CD] and [amine] corrected for the formation of the {CD·amine} complex (eq 7). To find these concentrations, we make use of the definition of K_N and the mass balance for the species in eq 7 and solve the quadratic in [CD] obtained by the expansion of: $K_N = [CD][Nuc]/[CD{\cdot}Nuc] = [CD]([Nuc]_o - [CD]_o + [CD])/([CD]_o - [CD])$. The required solution of the quadratic is $[CD] = \{ -b + (b^2 + 4K_N[CD]_o)^{1/2}\}/2$, where $b = (K_N - [CD]_o + [Nuc]_o)$. By difference, $[Nuc] = [Nuc]_o - [CD{\cdot}Nuc] = [Nuc]_o - ([CD]_o - [CD])$.

Binding Studies. The data analysis required the dissociation constants of the CD complexes of the esters and the amines. Values of K_S were taken from earlier studies,[7,8] and most of the K_N values for the amines binding to β-CD and hp-β-CD were determined previously using displacement of a fluorescent probe.[14b] Additional values were obtained using a spectral displacement method[30] based on the complexation of the dye phenolphthalein (PP).[31]

From the decreases in absorbance of 50 μM PP at three wavelengths (542, 552, and 562 nm), brought about by the addition of the CD (0−5.00 mM, nine concentrations), K_d values for the complexation of PP were determined to be 0.112 ± 0.002 mM for β-CD, 0.117 ± 0.002 mM for hp-β-CD, and 1.24 ± 0.04 mM for γ-CD, in the 0.20 M aqueous phosphate buffer of pH 11.6, at 25° C. The values found for β-CD and γ-CD are about twice those found earlier at lower pH (10.0−10.5) in weak carbonate buffers[31] which is not unreasonable given the different media.

The K_d values for PP binding were used in competition experiments to estimate K_N values for amine binding. To test the methodology, we studied the displacement of PP from β-CD and hp-β-CD by *n*-butylamine and *n*-pentylamine. Analysis of the spectral changes[32] caused by these amines gave values of K_N in excellent agreement with those found earlier[14b] for β-CD, using the fluorescent probe method, but for hp-β-CD the agreement was not quite as good (see Table 1, footnote c). Application of the method to the binding of isobutylamine, isopentylamine, and benzylamine to β-CD and hp-β-CD gave the values of K_N presented in Table 1.

The binding of amines to α-CD was studied using *p*-nitrophenoxide ion ($pNPO^-$) as a UV-visible spectral probe. From analysis of the increases in absorbance at five wavelengths (415, 417, 420, 425, 430 nm) with [α-CD] (0−10 mM, 10 concentrations), the average K_d for the complex of $pNPO^-$ was determined to be 0.732 ± 0.010 mM, in 0.20 M aqueous phosphate buffer of pH 11.6. This value is just outside the range of most of the literature values, which range from 0.28 to 0.63 mM, but which were obtained at lower pH, in weak buffers, and by various means.[30] Using K_d = 0.732 mM for $pNPO^-$, and the changes in absorbance in the range 415−420 nm brought about by added amines, values of K_N for the amines and α-CD were estimated (Table 1).[32]

Attempts to probe the binding of amines to γ-CD using the displacement of phenolphthalein were unsuccessful (cf. ref 31e), and so we developed a method based on induced circular dichroism (icd).[33] Measurement of the icd signal of the probe molecule ANS at 276 nm as a function of [γ-CD] led to a K_d of 7.04 ± 0.28 mM, in very good agreement with the value of 7.81 ± 0.17 mM found by fluorescence measurements.[14b] Using K_d = 7.04 mM, and the reductions in the icd spectra caused by added amines, values of K_N for amines binding to γ-CD were estimated (Table 1). Again, analysis of the data was virtually the same as that used for the displacement of absorbance (see above) and fluorescence probes.[14b]

It should be noted that if a K_N value was to be in serious error, for whatever reason, then the data analysis based on eq 6 would not work well. This situation only seemed to arise for the reactions of pNPA and pNPH by cyclohexylamine in the presence of hp-β-CD where K_N = 5.21 mM (determined twice)[14b] gave poor data analyses. Better analyses could be obtained with a K_N value of 1.8 mM, close to that for β-CD.

Acknowledgment. We thank the Natural Sciences and Engineering and Research Council of Canada for an operating grant, a post-graduate scholarship (to T.A.G.) and an equipment grant toward the purchase of the stopped-flow spectrophotometer. We are also grateful to Dr. Joanne Turnbull for the use of the circular dichroism spectrometer and to Mr. Craig Fenwick for running electrospray mass spectra. We also thank Prof. R. A. McClelland (University of Toronto) for helpful, critical comments.

JO9919660

(30) Connors, K. A. *Binding Constants: The Measurements of Molecular Complex Stability*; Wiley-Interscience: New York, 1987.

(31) (a) Buvari, A.; Barcza, L. *Inorg. Chim. Acta* **1980**, *33*, L179. (b) Taguchi, K. *J. Am. Chem. Soc.* **1986**, *108*, 2705. (c) Buvari, A.; Barcza, L.; Kajtar, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1687. (d) Sasaki, K. J.; Christian, S. D.; Tucker, E. E. *J. Colloid Interface Sci.* **1990**, *134*, 412. (e) Gray, J. E.; MacLean, S. A.; Reinsborough, V. C. *Aust. J. Chem.* **1995**, *48*, 551.

(32) The data analysis for the spectral displacement method is essentially identical to that developed for the displacement of a fluorescent probe.[14b]

(33) The chromophores of an achiral guest bound to a chiral host, such as a CD, can exhibit induced circular dichroism[12,34] (icd) and measurement of icd spectral changes as a function of [host] have been used to estimate host−guest binding constants.[35]

(34) Shimizu, H.; Kaito, A.; Hatano, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 513. Kodaka, M.; Fukaya, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1154. Yoshida, N.; Yamaguchi, H.; Higashi, M. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 2507. Meyer, B.; Marconi, G.; Klein, C.; Köhler, G.; Wolschann, P. *J. Incl. Phenom.* **1997**, *29*, 79.

(35) Bowen, J. M.; Purdie, N. *Anal. Chem.* **1981**, *53*, 2239. Han, S. M.; Atkinson, M.; Purdie, N. *Anal. Chem.* **1984**, *56*, 2827.