Catalysis by Cyclodextrins in Nucleophilic Aromatic Substitution Reactions. 2.[1] Amines as Nucleophiles[2]

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The kinetics of the reactions of 1-chloro-2,4-dinitrobenzene and 1-fluoro-2,4-dinitrobenzene with piperidine, butylamine, and morpholine in the presence of β-cyclodextrin (CD) was studied. There is an increase in the observed rate constant for the reactions of the first two amines at pH < pK_{AH} when CD is added, but there is no change in rate for these two reactions at pH > pK_{AH} and for the reaction of morpholine either at pH < pK_{AH} or at pH > pK_{AH}. The three amines (A) as well as their conjugated acids (AH) form inclusion complexes with the CD. The association equilibrium constants for the amines are 50, 3, and 17 M^{-1} for piperidine, butylamine, and morpholine, respectively. Part of the observed catalysis is attributed to the fact that the amines and the complexed amines (ACD) react with the substrate at similar rates and at constant pH, the ratio (A + ACD)/(AH + AHCD) increases with the concentration of CD. Besides that, the complexed substrates react with the complexed amines at faster rates than that of the free substrate with the free amine. The latter reaction is not detected in the reactions at high pH and in the reactions of morpholine.

Cyclodextrins are cyclic oligomers of α-D-glucose which are produced by enzymatic degradation of starch. They have a cavity of well-defined dimensions formed by two CH rings of the glucose units and a ring of the glycosidic oxygens.[3] The secondary and primary OH are located outside the cavity, thus the interior of the cavity is relatively apolar compared to water. A great variety of compounds form inclusion complexes with this type of molecules, and as a result of the interaction many reactions have been found to be catalyzed[4] and also inhibited.[5]

We recently reported the effect of β-cyclodextrin (CD) on the hydrolysis reaction of 1-X-2,4-dinitrobenzene 1 (X = F and Cl), and we found that the rate of consumption of the substrate is accelerated by two independent mechanisms. One of them involves the nucleophilic reaction of ionized CD with the aromatic substrate, and the other is the hydrolysis of the substrate catalyzed by a microsolvent effect.[1]

Since we found that the substrates studied form inclusion complexes with CD we thought to be of interest to study these reactions with organic nucleophiles which could also form inclusion complexes with CD. The reactivity of the included nucleophiles is not expected to be the same as that of the nucleophiles in the bulk solution thus it could be possible to change the selectivity of a pair of nucleophiles reacting with one electrophile. This expectation is borne out by the reaction of butylamine described below.

Moreover there exist the possibility, when the cavity size is large enough, that both species, electrophile and nucleophile, complex together with the host, resulting in an increase in rate due to a proximity effect similar to that responsible for catalysis by enzymes.[6]

We report here on our studies of the reactions of the substrates 1 with butylamine, piperidine, and morpholine which have been found to form inclusion complexes with CD and react with the complexed substrates at faster rates.

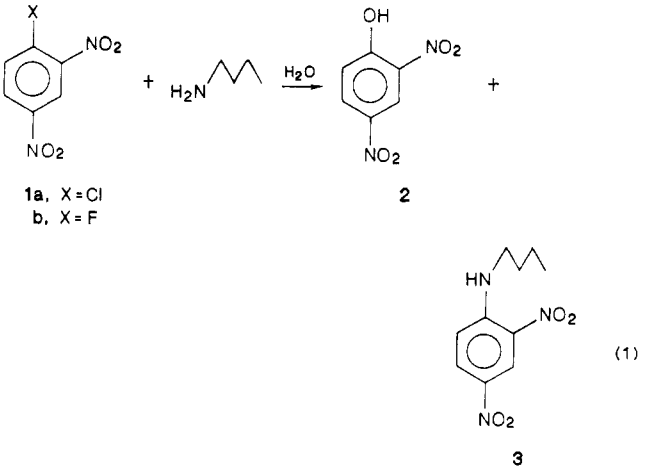
Table I. Reaction of 1-Chloro-2,4-dinitrobenzene with Butylamine in the Presence of β-Cyclodextrin[a]

$10^2[CD]_0$, M	10^5k_{obsd}, s^{-1}	% 3[b]	3/2[c]
	7.60	74.3	2.89
0.05	7.75	71.5	2.51
0.10	7.76	69.0	2.23
0.50	8.30	62.7	1.68
1.00	9.20	58.7	1.40

[a] The solvent contains water–dioxane (9:1, v/v); T = 25 °C; ionic strength, 0.2 M; $[S]_0 = 4.5 \times 10^{-5}$ M; $[NaOH]_0$ = 0.1 M; $[butylamine]_0$ = 0.05 M. [b] Yield of the aminolysis product. [c] Ratio of the percentage of the aminolysis and hydrolysis products.

Results

The reaction of butylamine with 1-chloro-2,4-dinitrobenzene (**1a**) at pH 13 leads to the formation of 2,4-dinitrophenol (**2**) and *N*-butyl-2,4-dinitroaniline (**3**) (eq 1).



At constant pH, the ratio 3/2 decreases with the concentration of CD (Table I). This result is a consequence of the fact that the pseudo-first-order rate constant for the aminolysis remains constant at this pH, whereas the pseudo-first-order rate constant for the hydrolysis reaction increases. This reaction was not investigated further due to the low reactivity of butylamine which made the study at low pH inconvenient.

In the reaction of piperidine with **1a** at pH 11.27 the only product formed is *N*-(2,4-dinitrophenyl)piperidine (**4**). The hydrolysis reaction does not compete under these conditions because piperidine is about 25 times more reactive

(1) The first paper of this series: de Rossi, R. H.; Barra, M.; de Vargas, E. B. *J. Org. Chem.* **1986**, *51*, 2157.
(2) This results were presented in part at the 8th IUPAC Conference on Physical Organic Chemistry, Tokyo, Japan, 1986.
(3) For recent reviews, see: Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1977. Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344. Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. Sirlin, C. *Bull. Soc. Chim. Fr.* **1984**, II-5. Tabushi, I.; Kuroda, Y. In *Advances in Catalysis*; Academic: New York, 1983; Vol. 32, p 417.
(4) Bonora, G. M.; Fornasier, R.; Scrimin, P.; Tonellato, V. *J. Chem. Soc., Perkin Trans. 2* **1985**, 367. Breslow, R.; Trainor, G.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 273.
(5) Matsue, T.; Tasaki, Ch.; Fujihira, M.; Osa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1305.
(6) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.

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Table II. Reactions of 1-Chloro-2,4-dinitrobenzene with Piperidine in the Presence of β-Cyclodextrin[a]

	$[Pip]_0$,[b] M	$[Pip]_{free}$,[c] M	$[CD]_0$,[d] M	$10^3[CD]_{free}$,[e] M	10^3k_{obsd}, s^{-1}	10^2k_A,[f] M^{-1} s^{-1}
1	0.15[g]	0.0883			2.60	2.94
2	0.15[g]	0.0835	0.01	1.84	3.89	4.67
3	0.20[g]	0.113	0.01	1.43	5.81	5.14
4	0.26[g]	0.148	0.01	1.13	7.30	4.93
5	0.34[g]	0.195	0.01	0.883	10.20	5.27
6	0.022[h]	1.03×10^{-3}	0.001	0.897	0.0258	2.50
7	0.022[h]	1.02×10^{-3}	0.004	3.59	0.0478	4.69
8	0.022[h]	1.00×10^{-3}	0.007	6.29	0.0608	6.08
9	0.022[h]	0.99×10^{-3}	0.010	9.00	0.0781	7.89
10	0.10[i]	0.0237	0.0005	0.205	0.778	3.29
11	0.10[j]	0.0181	0.004	1.85	0.693	3.83
12	0.10[k]	0.0164	0.007	5.01	0.757	4.62
13	0.10[l]	0.0132	0.010	5.21	0.743	5.63

[a] Solvent contains water/dioxane (9:1, v/v); $[S]_0 = (3.5–4.5) \times 10^{-5}$ M; ionic strength, 0.2 M; T = 25 °C. [b] Stoichiometric piperidine concentration. [c] Uncomplexed piperidine concentration calculated from eq 9 with $K_{AH} = 7.60 \times 10^{-12}$ (Bernasconi, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 129), $K_{CD}^{A} = 51$ M^{-1}, $K_{CD}^{AH} = 3$ M^{-1}, $[H^+]$ = antilog (-pH). [d] Added β-cyclodextrin concentration. [e] Uncomplexed β-cyclodextrin concentration calculated from eq 11. [f] $k_{obsd}/[Pip]_{free}$. [g] pH 11.275. [h] pH 9.814. [i] pH 10.613. [j] pH 10.476. [k] pH 10.442. [l] pH 10.326.

Table III. Reactions of 1-Fluoro-2,4-dinitrobenzene with Butylamine in the Presence of β-Cyclodextrin[a]

$[BuNH_2]_0$,[b] M	$10^2[CD]_0$,[c] M	10^4k_{obsd}, s^{-1}	f_A[d]	10^4k_A,[e] s^{-1}
0.001[f]		5.42	0.62[g]	3.36
0.001[f]	1.00	15.2	0.28[h]	4.27
0.022[i]		2.65	0.97	2.57
0.022[j]	0.049	3.24	0.98	3.18
0.022[j]	0.106	3.57	0.97	3.46
0.022[j]	0.298	3.72	1.0	3.72
0.022[j]	0.503	4.15	0.97	4.03
0.022[j]	0.503	3.65	0.99	3.61
0.022[j]	0.700	4.23	0.98	4.15
0.022[j]	0.881	4.87	0.96	4.68
0.022[j]	1.00	5.10	0.99	5.05

[a] Solvent contains water/dioxane (9:1, v/v); $[S]_0 = (4–5) \times 10^{-5}$ M; ionic strength, 0.2 M. [b] Total initial butylamine concentration. [c] Total β-cyclodextrin added. [d] Fraction of the aminolysis product. [e] Pseudo-first-order rate constant for aminolysis. [f] [NaOH] = 0.001 M added. [g] 38% of 2,4-dinitrophenol also formed. [h] 8% of 2,4-dinitrophenol formed. The rest of the substrate is consumed by reaction with the β-cyclodextrin. [i] pH 9.252. [j] pH 9.303.

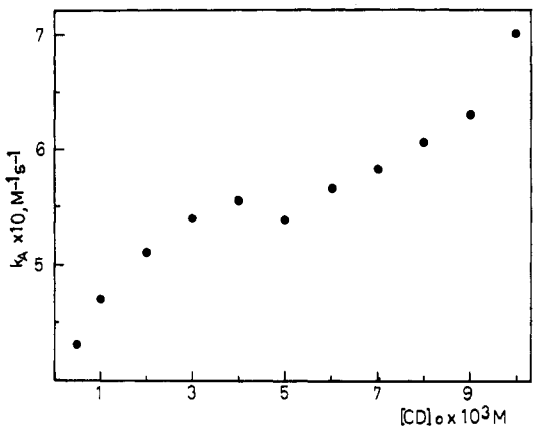


Figure 1. Second-order rate constant, k_A, for the aminolysis of **1b** vs. β-cyclodextrin concentration. Data were obtained at pH between 10.3 and 9.3, at 25 °C, ionic strength 0.2 M.

than butylamine. At constant pH and CD concentration the second order rate constant remains aproximately the same when the concentration of piperidine increases (Table II, runs 2–5), the average value is 5×10^{-2} M^{-1} s^{-1}, which is higher than the second-order rate constant for the same reaction in the absence of CD. In runs 6–9 (Table II) the solutions were equilibrated at the same pH to avoid uncertainties in the calculation of the free amine concentration due to changes in the pK of the amine because of the presence of dioxane.[7] It can be seen that the observed rate constant increases from 2.58×10^{-5} s^{-1} at [CD] = 0.001 M to 7.81×10^{-5} s^{-1} at [CD] = 0.01 M, which demonstrates that the observed catalysis is real.

In the reaction of butylamine with 1-fluoro-2,4-dinitrobenzene (**1b**) at pH ~11 (Table III) the aminolysis product **3** and also the hydrolysis product **2** are formed competitively, besides in the presence of CD it also reacts with this substrate as was previously observed,[1] and then we conducted most of our studies at a pH where more than 90% of the aminolysis product is formed. In Table III it can be seen that the pseudo-first-order rate constant k_{obsd} increases regularly as the concentration of CD increases. In Figure 1 the data of Table III together with some additional data are plotted vs the CD concentration. Figure 1 shows that there is a sigmoidal dependence of the second-order rate constant of this reaction with the CD concentration.

Although the number of points is more limited in the case of the reaction of **1a** with piperidine the same trend is observed; i.e., the plot (not shown) of the observed rate constant vs. the CD concentration is sigmoidal.

The reaction of **1b** with piperidine at pH 9.6 gives **4** as the only product. The addition of CD at constant total amine concentration increases the observed rate. Again, as we have seen before there is a sigmoidal dependence between the observed rate constant and the concentration of CD. The same reaction at pH 12.2 gives over 90% of the aminolysis product, but the observed rate constant *does not* change with the concentration of CD. Similar result is observed in the reaction of **1a** with piperidine (Table II, runs 10–13) however in both cases if the concentration of the free amine is calculated, and the observed rate constant is divided by this concentration, the value of k_A, the second-order rate constant for the reaction of the free amine with the free substrate increases. This is shown in the last column of Table II for substrate **1a**. For substrate **1b**, k_A increases from 15 to 22 M^{-1} s^{-1}.

For comparative purposes, the effect of the addition of starch which is a linear analogue of CD, was studied. In Table IV, runs 10–12, it can be seen that this polysaccharide slightly decreases the rate.

The reaction of morpholine with **1b** is not influenced in any way by the presence of CD at pH 10.38 whereas at pH 7.31 there is an increase which is barely outside experi-

(7) It has been determined that β-cyclodextrin affect the measured pH (ref 8); however, under the conditions of our studies the correction was not applied because it is negligible.

(8) Gelb, R. I.; Schwartz, L. M.; Johnson, R. F.; Laufer, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1869.

Table IV. Reactions of 1-Fluoro-2,4-dinitrobenzene with Piperidine[a]

	$10^2[CD]_0$, M	$[CD]_{free}$,[b] M	$10^4[Pip]_{free}$,[c] M	$10^4[ACD]$,[d] M	10^3k_{obsd}, s^{-1}
1			6.50		4.24
2	0.05[e]	0.456	6.49	0.151	4.73
3	0.10[e]	0.911	6.48	0.301	5.50
4	0.28[e]	2.55	6.43	0.836	8.08
5	0.46[e]	4.20	6.39	1.37	10.2
6	0.64[e]	5.85	6.34	1.89	11.7
7	0.82[e]	7.49	6.30	2.41	13.1
8	1.0[e]	9.14	6.25	2.91	15.5
9	*f*				9.0
10	0.05[f,g]				9.0
11	0.46[f,g]				8.3
12	1.00[f,g]				7.1
13	1.00[f,h]				13.0
14	*f*,*i*				34.2
15	0.25[f,i]				42.0
16	0.50[f,i]				51.3
17	1.00[f,i]				68.0

[a] Solvent contains water/dioxane (9:1, v/v); $[S]_0 = 4.5 \times 10^{-5}$ M; $[Pip]_0 = 0.022$ M; ionic strength, 0.2 M; $T = 25$ °C. [b] Uncomplexed β-cyclodextrin calculated with $K_{CD}^{A} = 51$ M^{-1}, $K_S = 2 \times 10^3$ M^{-1}. [c] Uncomplexed piperidine calculated with the $K_{CD}^{AH} = 3$ M^{-1}, $K_{AH} = 7.6 \times 10^{-12}$ M and K_{CD}^{A} as in *b*. [d] Complexed piperidine. [e] pH 9.603. [f] pH 9.876. [g] Soluble starch instead of β-cyclodextrin is added. [h] γ-Cyclodextrin instead of β-cyclodextrin is added. [i] The substrate is 1-chloro-2,4,6-trinitrobenzene.

Table V. Reactions of 1-Fluoro-2,4-dinitrobenzene with Morpholine in the Presence of β-Cyclodextrin[a]

$10^3[CD]_0$,[c] M	10^3k_{obsd},[d] s^{-1}	$10^3[CD]_0$,[c] M	10^3k_{obsd},[d] s^{-1}
	$[Morp]_0$[b] = 10^{-3} M; pH 10.385		
	1.07	7.0	1.15
1.0	1.19	10.0	1.24
4.0	1.33		
	$[Morp]_0$[b] = 0.022 M; pH 7.315		
	1.24	6.00	1.31
1.21	1.23	7.00	1.34
2.02	1.30	8.02	1.32
3.00	1.29	9.00	1.34
4.01	1.39	10.00	1.41
4.99	1.30		

[a] Solvent contains water/dioxane (9:1, v/v); $T = 25$ °C; ionic strength, 0.2 M; $[S]_0 = (4.5\text{–}5.0) \times 10^{-5}$ M. [b] Total initial morpholine concentration. HCl added to adjust the pH. [c] Initial β-cyclodextrin concentration. [d] Observed rate constant times the fraction of the aminolysis product, which in all cases is higher than 90%.

mental error (Table V); however, as we have seen before the second-order rate constant increases.

Determination of Association Constants between the Amines and Cyclodextrin. The equilibrium constant for the formation of an inclusion complex between the amines and CD was determined by a competition method using *p*-nitroaniline as indicator.[9] This method is based on the competition between the indicator and the amine for the host (eq 2 and 3).

$$\text{In} + \text{CD} \rightleftharpoons \text{InCD} \qquad K_{In} = \frac{[\text{InCD}]}{[\text{In}][\text{CD}]} \tag{2}$$

$$\text{A} + \text{CD} \rightleftharpoons \text{ACD} \qquad K_{CD}^{A} = \frac{[\text{ACD}]}{[\text{A}][\text{CD}]} \tag{3}$$

The association constant of the indicator K_{In} was first measured by determining the change in absorbance at 404 nm of solutions of constant *p*-nitroaniline concentration and increasing concentration of CD. The data were then

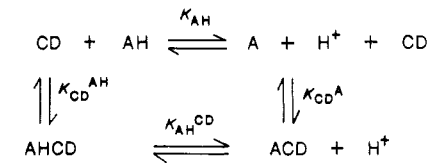
(9) Tabushi, I.; Kuroda, Y.; Mizutami, T. *J. Am. Chem. Soc.* **1986**, *108*, 4514.

Table VI. Association Constants of Amines with β-Cyclodextrin

amine	conc, M	K_{CD}, M^{-1}
piperidine[a]	$(7\text{–}70) \times 10^{-3}$	49
piperidine[a]	$(1.3\text{–}6.5) \times 10^{-2}$	53
piperidine[b]	$(9.4\text{–}6.5) \times 10^{-3}$	<3
butylamine[a]	$(1.7\text{–}8.6) \times 10^{-2}$	3
morpholine[a]	$(1.1\text{–}10) \times 10^{-2}$	17
morpholine[b]	$(1.1\text{–}10) \times 10^{-2}$	7

[a] pH ~13. [b] pH ~7.

Scheme I



plotted as in the Benesi–Hildebrand method,[10] and from the ratio of the slope and intercept of this plot, the equilibrium constant was obtained. This value is 260 M^{-1}, which is somewhat higher than the value reported in the literature, 160 M^{-1}.[11] The equilibrium constants for butylamine, piperidine, and morpholine and that of their conjugated acids were determined by measuring the change in absorbance of the InCD complex as the concentration of the amine (or its conjugated acid) increases. The data obtained and experimental conditions for their determinations are summarized on Table VI.

Since at the wavelength of observation there is no absorption by A or ACD, K_{CD}^{A} (or K_{CD}^{AH}) can be evaluated from eq 4 and 5 where ΔOD is the change in absorbance when the amine is added and $\Delta\epsilon$ is the difference in extinction coefficients of In and InCD which were independently determined.

$$[\text{CD}] = [-\{1 + K_{CD}^{A}([\text{A}]_o - [\text{CD}]_o)\} + [\{1 + K_{CD}^{A}([\text{A}]_o - [\text{CD}]_o)\} + 4K_{CD}^{A}[\text{CD}]_o]^{1/2}]/2K_{CD}^{A} \tag{4}$$

$$\Delta\text{OD} = \frac{\Delta\epsilon K_{In}[\text{In}]_o[\text{CD}]}{1 + K_{In}[\text{CD}]} \tag{5}$$

The experiences were done under conditions where the free amine or the corresponding ammonium ions were the predominant species, but the only value for an ammonium ion that could be measured was that of morpholine. In the case of piperidine and butylamine we can only say that the equilibrium constant for reaction **3** when A = $C_5H_{10}NH_2^+$ or $C_4H_9NH_3^+$ is smaller than 3.

We attempt to determine these equilibrium constants by potentiometric titration as described in the literature.[12] In this case the equilibria involved are shown in Scheme I.

The apparent dissociation constant of the amine in the presence of CD can be expressed as in eq 6. Then from the measurement of the pH at half-titration of solutions of the amine and CD, the values of K_{CD}^{A} and K_{CD}^{AH} can be calculated.

$$K_{app} = \frac{([\text{A}] + [\text{ACD}])[\text{H}^+]}{([\text{AH}] + [\text{AHCD}])} = K_{AH}\frac{(1 + K_{CD}[\text{CD}])}{(1 + K_{CD}^{AH}[\text{CD}])} \tag{6}$$

This method gives significantly higher values than the indicator method described above, for instance for piperidine $K_{CD}^{A} = 200$ M^{-1}.[13]

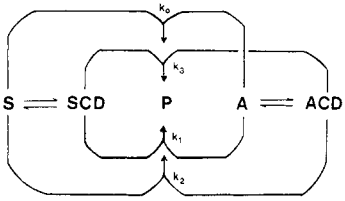
(10) Benesi, A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
(11) Wang, Y.; Eaton, D. F. *Chem. Phys. Lett.* **1985**, *120*, 441.
(12) Connors, K. A.; Lin, S.; Wong, A. B. *J. Pharm. Sci.* **1982**, *71*, 217.

Table VII. Effect of β-Cyclodextrin on the Concentration of Piperidine, Free and Complexed[a]

pH	$[CD]_0$, M	$[A]/[A]_0$	$[ACD]/[A]_0$	$[AH]/[A]_0$	$[AHCD]/[A]_0$
9.603		0.0295[b]		0.970	
9.603	0.01	0.0284[b]	0.0132	0.932	0.0264
12.00		1[c]			
12.00	0.01	0.615[c]	0.385		

[a] Calculated with $K_{CD}^{A} = 51\ M^{-1}$, $K_{CD}^{AH} = 3\ M^{-1}$, $K_{AH} = 7.60 \times 10^{-12}$. [b] Calculated with $[A]_0 = 0.022$ M. [c] $[A]_0 = 0.01$ M.

Scheme II



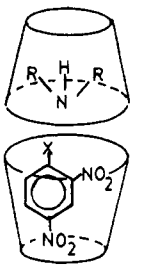
Discussion

Since the amine as well as the ammonium ion form inclusion complexes with CD, but the equilibrium constants for both species are different, in a buffer solution of amine and ammonium ion the amount of total amine, free and complexed, changes as the CD increases. This effect is illustrated in Table VII where the concentration of the involved species are calculated.

Table VII shows that the amount of free amine A changes very little at pH < pK_{AH} but at high pH (pH > pK_{AH}) it decreases by about 30%. It would then be expected that in the absence of any other effect the rate of aminolysis remains aproximately constant at low pH and decreases at high pH which is contrary to our experimental results. On the other hand the amount of (A + ACD) at constant pH and constant amine concentration increases as the CD concentration increases so if both species react at similar rates with the substrate the change in rate should parallel the increase in the sum (A + ACD). This effect is observed in the reaction of 2,4,6-trinitrochlorobenzene with piperidine where the ratio of the pseudo-first-order rate constants for 0.01 M and zero concentration of CD is 2. Under these conditions the ratio between the (A + ACD) and A concentrations at the same pH is 1.54, whereas the ratio of observed rate constants for the reaction of piperidine with **1b** is 3.6. This indicates that there must be another factor besides the increase in concentration of the reactive species which contribute to increase the rate. We know from previous work that **1a** as well as **1b** form inclusion complexes with CD,[1] now we have determined that piperidine, butylamine, and morpholine are included by CD, thus we suggest that our kinetic scheme may be represented as in Scheme II where the possibility of reactions of the free substrate (S) with the free amine (A), the complexed substrate (SCD) with the free amine (A), or its kinetically equivalent reaction of the free substrate with the complexed amine (ACD) and the complexed substrate and complexed amine are represented.

The rate of the reaction is given by eq 7 and the concentration of the species involved are given by eq 8–11. K_S is the association equilibrium constant of the substrate (**1a** or **1b**) and K_{CD}^{AH}, K_{CD}^{A}, and K_{AH} are defined in Scheme I. Combining eq 7–11, the observed pseudo-first-order rate constant is obtained (eq 12).

Scheme III



$$v = \frac{d[S_T]}{dt} = k_o[S][A] + k_1[S][ACD] + k_2[SCD][A] + k_3[SCD][ACD] \quad (7)$$

$$[S]_T = [S] + [SCD] = [S]_o(1 + K_S[CD]) \quad (8)$$

$$[A]_o = [A] + [AH] + [ACD] + [AHCD] = [A]\{1 + [H^+]/K_{AH} + [CD](K_{CD}^{A} + K_{CD}^{AH}[H^+]/K_{AH})\} \quad (9)$$

$$[ACD] = K_{CD}^{A}[A][CD] \quad (10)$$

$$[CD]_o = [CD] + [ACD] + [AHCD] + [SCD][CD] + [ACD] + [AHCD] = [CD]\left[1 + \frac{K'K_{AH}[A]_o}{K_{AH} + [H^+] + K'K_{AH}[CD]}\right] \quad (11)$$

$$K' = K_{CD}^{A} + K_{CD}^{AH}[H^+]/K_{AH}$$

$$k_{obsd} = \{[k_o + (k_1K_{CD}^{A} + k_2K_s) \times [CD] + k_3K_SK_{CD}^{A}[CD]^2][A]_o\}/\{1 + [H^+]/K_{AH} + [K' + K_S(1 + [H^+]/K_{AH})][CD] + K_SK'[CD]^2\} \quad (12)$$

Since k_o and all the equilibrium constants are known, we could calculate k_3 and the sum $k_1K_{CD}^{A} + k_2K_S$ by nonlinear adjustment of the data to eq 12.[14] Since $K_S \gg K_{CD}^{A}$ for piperidine and butylamine the sum must be equated to k_2K_S unless $k_1 \gg k_2$, and thus we could estimate $k_2 = 0.4\ M^{-1}\ s^{-1}$ for butylamine and $8.5\ M^{-1}\ s^{-1}$ for piperidine and $k_3 = 12$ and $37\ M^{-1}\ s^{-1}$ for butylamine and piperidine, respectively. The k_2 values in both cases are similar to the corresponding values for the second-order rate constants in the absence of CD, namely, 0.34 and 6.5 $M^{-1}\ s^{-1}$. Thus we can conclude that there is not a big free energy difference in the transition state for the reaction of the substrates with the amines in the bulk solution or with the complexed substrate. This result is consistent with the fact that in the reaction of **1a** with piperidine a change in solvent from 10% to 60% dioxane/water does not produce any change in rate.[15] On the other hand there is an important decrease in free energy when the complexed substrate and complexed amine react together. This may be due to the possibility of formation of channel-like structures of CD units[16] which serve to fix the reacting species in close proximity or to the formation of a complex between ACD and SCD as shown in Scheme III. Similar types of complexes have been previously demonstrated, for instance a naphthalene–CD complex associates with an *o*-dicyanobenzene–CD complex with an equilib-

(13) We do not know the reasons of this discrepancy. To compare the potentiometric method with the indicator method, we determined the equilibrium value $K_{CD}^{A} = 2 \times 10^3\ M^{-1}$ for adamantanamine using *p*-nitroaniline as indicator; this value is much lower than the value reported, namely, $10^5\ M^{-1}$ (see: Gelb, R. I.; Schwartz, L. M.; Laufer, D. A. *J. Chem. Soc., Perkin Trans. 2* **1984**, 15).

(14) Computer calculations were done on a Vax 11 computer by using a derivative-free nonlinear regression program obtained from the the Department of Biomathematics, University of California, Los Angeles.

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rium constant of 3.2×10^3 M^{-1}.[17]

The fact that at high pH the observed pseudo-first-order rate constants are independent of the CD concentration indicates that both species, the amine and complexed amine, react at similar rates with the substrate. Besides at this pH there is not a significant contribution of the k_3 step, and this effect may be attributed to the fact that at this pH a significant fraction of the CD is ionized and electrostatic repulsion prevents the aproximation of the two included reactants.

We have studied the reaction of piperidine with **1b** in the presence of γ-cyclodextrin (which has eight glucose units) because its cavity size is bigger than that of CD therefore it could be possible that electrophile and nucleophile complex together resulting in a greater effect on the rate. As it can be seen in Table IV comparing runs 8 and 13 the change of β-cyclodextrin by γ-cyclodextrin does not produce any significant change in rate; however, this experiment alone does not discard the possibility of formation of mixed complexes, it only indicates that either they are formed in very low quantity or in the mixed complex the reactants do not have the appropriate orientation to favor the reaction.

The lack of catalysis in the reactions of morpholine may be due in part to the fact that the association constants of the amine and its conjugated acid are similar and thus there is little change in concentration of the active nucleophile at constant pH. It also indicates that in this reaction there is no contribution by the k_3 step, which may be attributed to the orientation of the amine in the cavity of the CD. It must be noted that the relative contribution of the k_3 step decrease in the order butylamine > piperidine ≫ morpholine.

Conclusions

We found that when the substrates **1a** and **1b** are complexed with CD, they react with butylamine, piperidine, and morpholine at rates similar to those of the uncomplexed substrates with the amines in the bulk solution. This indicates that the electrophiles **1a** and **1b** in the complex are not located far down in the cavity, so the approach of the nucleophile is not sterically hindered, and the microenvironment around the reaction center is similar to that in the bulk solution.

As the amines form stronger complexes with CD than their conjugated acids, at constant pH, there is an increase in the total amount of nucleophile (A + ACD). When CD is added the observed pseudo-first-order rate constant increases as the concentration of CD increases; however, the rate is enhaned more than it would be expected on the bases of the change in the total concentration of (A + ACD). We atribute this effect to the participation of a reaction pathway involving some kind of mixed complex between ACD and SCD as shown in Scheme III.

This reaction pathway appears to contribute more in the reaction of butylamine than in the reaction of piperidine and much less in the reaction of morpholine, indicating different orientation of the amines in the cavity.

Experimental Section

Aqueous solutions were made up from water purified in a Millipore apparatus. Dioxane was purified as described previously.[18]

β-Cyclodextrin and soluble starch were purchased from Sigma and used as received. γ-cyclodextrin Aldrich was a generous gift from Dr. F. Menger. 1-Chloro-2,4-dinitrobenzene and 1-fluoro-2,4-dinitrobenzene were purified as in previous work.[1] *N*-(2,4-Dinitrophenyl)piperidine and *N*-(2,4-dinitrophenyl)morpholine were compounds existing in the laboratory from previous work.[19] Piperidine and butylamine were refluxed 12 h over Na and distilled. Morpholine was purified by the method described by Perrin.[20]

pH measurements were carried out on a Corning 101 digital pH meter at 25 °C. Standard buffers prepared according to procedures described in the literature[21] were used to calibrate the electrode. The pH of the solutions indicated in the tables is the pH measured before the addition of dioxane.

Kinetic Procedures. Reactions were initiated by adding the substrate dissolved in dioxane to a solution containing all the other constituents. The total dioxane concentration was 10%. The reactions were run at 25 °C and at constant ionic strength using NaCl as compensating electrolyte. The observed rate constants, k_{obsd}, were determined by following the appearance of the aminolysis product.

The change in optical density during a kinetic run was recorded on a Beckman 24 spectrophotometer or on a Shimadzu 260 recording spectrophotometer at the maximum absorption of the products. The yield of the aminolysis and hydrolysis products were determined as indicated before.[22] All reactions were run under pseudo-first-order conditions and they were followed up to 80–90% conversion.

Equilibrium Constant Determinations. (a) Competition Method. All the equilibrium constants were determined in water solutions at 25 °C. A solution of *p*-nitroaniline (7.3×10^{-5} M) has an absorption maximum at 380 nm. The maximum shows a bathochromic shift when CD in the concentration range 1.2×10^{-4} to 0.01 M is added, and there is one isosbestic point at 373 nm, which indicates that only one type of complex is formed. The difference spectrum has its maximum at 404 nm, so this wavelength was chosen to measure the ΔOD. The relationship between ΔOD and the CD concentration is given by eq 13.

$$\frac{[\mathrm{In}]_o[\mathrm{CD}]_o}{\Delta \mathrm{OD}} = \frac{1}{K_{\mathrm{In}}\Delta\epsilon} + \frac{[\mathrm{CD}]_o}{\Delta\epsilon} \qquad (13)$$

The plot of $(\Delta OD)^{-1}$ vs. $[CD]^{-1}$ is linear, and from the slope and intercept $\Delta\epsilon$ and K_{In} were calculated as 2.8×10^3 M^{-1} cm^{-1} and 260 M^{-1}.

To determine the equilibrium constants of piperidine, butylamine, and morpholine and their respective conjugated acids, solutions containing constant concentration of the indicator and CD and variable concentration of the amine and ammonium ion were prepared, and the change in the optical density was measured. The concentration used are indicated in Table VI.

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Registry No. 1-Chloro-2,4-dinitrobenzene, 97-00-7; 1-fluoro-2,4-dinitrobenzene, 70-34-8; butylamine, 109-73-9; morpholine, 110-91-8; β-cyclodextrin, 7585-39-9; β-cyclodextrin–piperidine inclusion complex, 110014-18-1; β-cyclodextrin–morpholine inclusion complex, 110014-19-2; β-cyclodextrin–butylamine inclusion complex, 110014-20-5; β-cyclodextrin–piperidine (H^+) inclusion complex, 110014-21-6; β-cyclodextrin–morpholine (H^+) inclusion complex, 110014-22-7; β-cyclodextrin–butylamine (H^+) inclusion complex, 110026-31-8; β-cyclodextrin–2,4-dinitrochlorobenzene inclusion complex, 110014-23-8; β-cyclodextrin–2,4-dinitrofluorobenzene inclusion complex, 110014-24-9; piperidine, 110-89-4.

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