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Catalysis by Cyclodextrins in Nucleophilic Aromatic Substitution Reactions

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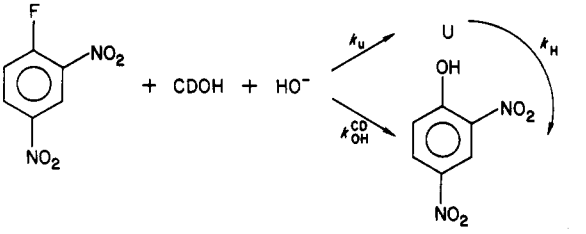
The kinetics of the hydrolysis of 1-X-2,4-dinitrobenzene (X = Cl, F) were studied in the presence of β-cyclodextrin. The overall rate of hydrolysis is catalyzed by the added compound, and the observed catalysis is pH dependent. For the reaction of the fluoro derivative the catalytic factor at 0.01 M β-cyclodextrin changes from 7 at 10^{-3} M NaOH to 2.5 at 10^{-1} M NaOH. Part of the catalysis is due to nucleophilic reaction of β-cyclodextrin with the substrate and part of it is attributed to the reaction of an inclusion complex formed between the substrate and the β-cyclodextrin. The catalytic factor corresponding to the reaction in the cavity is 1.4 and 2 for the fluoro and chloro derivative, respectively.

Cyclodextrins are cyclic oligomers of glucose with a doughnut shape and have a hydrophobic cavity. They are capable of forming host–guest complexes with a variety of organic compounds. The properties of these complexes have given rise to much interest, resulting in significant activity not only regarding the theoretical aspects of the interactions involved in the formation of these type of complexes and the catalysis of reactions but also regarding their applications in different areas such as agriculture and medicinal chemistry.[1]

Cyclodextrins have been found to catalyze the hydrolysis of a variety of compounds, such as phenyl esters and phosphate and phosphonate esters, and the catalysis involved is in most cases of the nucleophilic type. Cyclodextrins have two secondary HO and one primary HO for each glucose unit and a pK_a about 12.[2] The hydroxyl group reacts quite fast with the guest ester, thus increasing the rate of consumption of the substrate by factors that range from a few units to several orders of magnitude. In most of the different types of reactions studied, the catalysis is due to the covalent reaction between the cyclodextrin and the substrate.[3] In a few cases the catalysis was attributed to a microsolvent effect.[4]

To the best of our knowledge there have not been any studies of nucleophilic aromatic substitution reactions in the presence of cyclodextrins despite the fact that the mechanism of this reaction is well-known, and thus the effect of added cyclodextrins may shed light on the type of interaction leading to catalysis.

Scheme I



$k_u >> k_H$

We report here our studies of the reaction of 2,4-dinitrochloro- and 2,4-dinitrofluorobenzene in the presence of β-cyclodextrin (the member of 7 glucose units).[5]

Results

The hydrolysis of 1-fluoro-2,4-dinitrobenzene (1) and 1-chloro-2,4-dinitrobenzene (2) in water–dioxane (9/1 v/v) solutions and 0.2 M ionic strength led quantitatively to the formation of 2,4-dinitrophenol with second-order rate constants of 1.51×10^{-4} M^{-1} s^{-1} and 0.196 M^{-1} s^{-1}, respectively.

In the presence of 0.01 M β-cyclodextrin (CDOH), the reaction of 1 forms 2,4-dinitrophenol in an amount which varies with the concentration of HO^- (Table I). A compound which does not absorb at the wavelength maximum

(1) 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.

(2) Van Etten, R. L.; Clowes, G. A.; Sebastian, J. F.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3253.

(3) Van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242. Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762.

(4) Straub, T. S.; Bender, M. L. *J. Am. Chem. Soc.* **1972**, *94*, 8881, 8875.

(5) This work was presented in part at the Seventh IUPAC Conference on Physical Organic Chemistry, Auckland, New Zealand, August 20–24, 1984.

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Table I. Observed Rate Constants for the Hydrolysis of 2,4-Dinitrofluorobenzene as a Function of NaOH and β-Cyclodextrin Concentration[a]

no.	$(NaOH)_0 \times 10^2$ M	$(HO^-)_{eff} \times 10^2$ [b] M	$(CDOH)_0 \times 10^3$ M	$k_{obsd} \times 10^3$ s^{-1}	yield,[c] %
1	0.10	0.0622	10	0.809	18.7
2	0.40	0.259	10	3.18	19.8
3	0.70	0.471	10	5.52	20.6
4	1.0	0.695	10	6.48	22.0
5	2.5	1.95	10	17.9[d]	28.0
6	5.0	1.27	10	28.8[d]	37.2
7	7.5	6.69	10	37.0[d]	49.2
8	10	9.15	10	43.0[d]	56.1
9	0.10	0.0944	0.99	0.221	54.7
10	0.10	0.0892	2.0	0.346	41.1
11	0.10	0.0848	3.0	0.400	34.6
12	0.10	0.0805	4.0	0.493	29.7
13	0.10	0.0768	5.0	0.540	27.0
14	0.10	0.0733	6.0	0.583	24.1
15	0.10	0.0702	7.0	0.608	23.5
16	0.10	0.0673	8.0	0.678	21.9
17	0.10	0.0646	9.0	0.645	22.3
18	0.99	9.85	0.51	20.8[d]	95.5
19	0.99	9.80	1.0	25.2[d]	86.2
20	0.99	9.72	2.0	28.5[d]	79.9
21	0.99	9.55	4.0	33.2[d]	68.6
22	0.99	9.21	8.0	46.0[d]	55.2
23	0.50		10[e]	0.751	

[a] The solvent contains 10% v/v dioxane; ionic strength 0.2 M using NaCl as compensating electrolyte. Substrate concentration, 4.3–4.7 × 10^{-6}M. [b] Calculated from the stoichiometric concentration of NaOH and CDOH and the pK of CDOH ≈ 12.2 taken from ref 2. [c] Represents the yield of 2,4-dinitrophenol; the rest of the material is 2,4-dinitrophenylcycloheptaamilose. [d] Average of three or four determinations. The deviation among the different runs is less than 5%. [e] Maltose instead of β-cyclodextrin is added.

of 2,4-dinitrophenol is being formed in a parallel reaction. This compound in a later reaction slowly forms the phenol. Thus the kinetic behavior can be represented by Scheme I where k_u, k_{OH}^{CD}, and k_H are all pseudo-first-order rate constants.

The observed pseudo-first-order rate constants are thus given by eq 1, and from the determination of the fractional

$$k_{obsd}^{CD} = k_u + k_{OH}^{CD} \quad (1)$$

yield of products, k_u and k_{OH}^{CD} can be obtained.[6] For comparison purposes the rate of hydrolysis of 1 was measured in the presence of maltose; in this case the only product formed is 2,4-dinitrophenol, and there is a slight decrease in the rate (Table I no. 23).

The hydrolysis of **2**, in the presence of CDOH, leads quantitatively to the formation of 2,4-dinitrophenol under our experimental conditions. We could not detect any evident deviation from the strictly pseudo-first-order behavior when the reaction was carried out up to 1 half-life. These results seem to indicate that **2** behaved differetly from **1**, but the fact that the measured rates for **2** are in the same order of magnitude as the rate of hydrolysis of the unkonwn product isolated in the reaction of **1** (see below) shows that the formation of a similar compound might be undetected in the case of **2**. Thus the hydrolysis of **2** in the presence of CDOH could be represented as in Scheme I but with $k_H \approx k_u$.

The change in the observed optical density (OD) as a function of time for a kinetic scheme like Scheme I is given by eq 2 when the only absorbing species is the 2,4-dinitrophenol.

$$OD = \left[\frac{k_{OH}^{CD} - k_H}{k_H - (k_u + k_{OH}^{CD})} e^{-(k_u + k_{OH}^{CD})t} + \frac{k_u}{k_H - (k_u + k_{OH}^{CD})} e^{-k_{OH}^{CD} t} + 1 \right] (OD)_\infty \quad (2)$$

To calculate k_{OH}^{CD} we expanded this eq by a series of Maclaurin and adjusted the observed optical density to a polynomium of 1 to n degree until no more improvement within the observed and calculated values was obtained.[7] The value of k_{OH}^{CD} in Scheme I, that represents that part of the hydrolysis of the substrate which does not involve reaction between the substrate and CDOH, is calculated as the coefficient for the first-order term of the polynomium. The values of k_{OH}^{CD} for the hydrolysis of **2** thus calculated under different sets of conditions are collected in Table II. The ratio of these values to the one corresponding to the noncatalyzed reaction is 2:0; this indicates a weak catalysis.

We also determined the rate of hydrolysis of 2,4,6-trinitrochlorobenzene in the presence of 0.01 M CDOH, and we found no change in the rate at all. This result indicates that the observed change in the rate in the reaction of **2** cannot be attributed to modifications of the solvent produced by the presence of CDOH.

pH Dependence of the β-Cyclodextrin Rate Effect. The catalysis of the hydrolysis of both substrates **1** and **2** is pH dependent (see Table I and II), and this effect is particularly evident in the reaction of the fluoro derivative **1**.

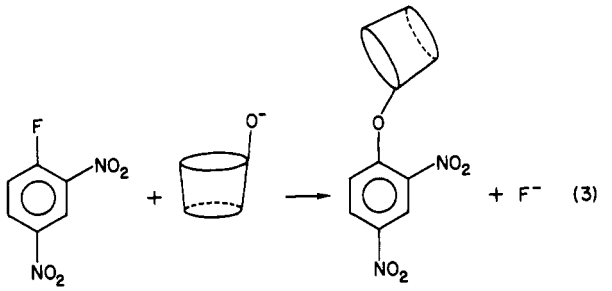
For the reaction of this substrate it can be seen that k_{OH}^{CD} increases linearly with the HO^- concentration (Figure 1) whereas k_u exhibits a first-order dependence at low OH^- concentration but it tends to level off at high HO^- concentration (Figure 2).

Since cyclodextrin has easily ionizable secondary OH groups (pK_a 12),[2] we thought that the unknown product might come from the reaction of 2,4-dinitrofluorobenzene with the alkoxide anion derived from β-cyclodextrin (eq 3). This would rationalize the dependence of the rate constant on the OH^- concentration in terms of an increased fraction of ionized β-cyclodextrin.

In an attempt to obtain a sample of 2,4-dinitrophenylcycloheptaamylose from a solution similar to the reaction

(6) Bunnett, J. F. *Techniques of Chemistry*; Lewis, E. S., Ed.; Wiley: 1974; Vol. 6, p 158.

(7) These calculations were carried out on a IBM 1130 computer. We thank Professor J. C. Ferrero for helping us with them.



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mixture, equivalent amounts of 1 and CDOH were mixed with an alkaline aqueous–dioxane solution. After 60 min, this mixture was neutralized and chromatographed on Sephadex G-10 (see Experimental Section), resulting in the separation of the unreacted substrate, the 2,4-dinitrophenol, and fractions containing cycloheptaamylose.

The UV absorption spectrum of the recovered cycloheptaamylose fractions showed the presence of a material having absorptions at 265 and 305 nm, coincident with the absorption maximum of a similar solution of 2,4-dinitroanisole.

When a solution of NaOH was added to the cycloheptaamylose fractions, the unknown product hydrolyzed forming 2,4-dinitrophenol at a rate equal to that measured when the product was formed "in situ", namely 3.62×10^{-4} M^{-1} s^{-1} and 3.43×10^{-4} M^{-1} s^{-1}, respectively, at 0.095 M NaOH.

Similar experiments carried out with 2 allowed the isolation of a compound with the same UV spectrum. (See Experimental Section).

From these results we conclude that U (Scheme I) is the 2,4-dinitrophenylcycloheptaamylose (3).

Inclusion Complex Formation. The UV spectrum of 1 is modified in the presence of 0.01 M CDOH (Figure 3). In the case of 2 there is a change in shape of the absorption band but no change is observed in the extinction coefficient. These results can be attributed to the formation of an inclusion complex between the substrate and CDOH (Scheme II).

The formation of a complex is also indicated by the fact that 1 and 2 can be extracted from their solutions in benzene when this solution is allowed to interact with an aqueous solution of CDOH. The increase in water solubility of 1 or 2 in the presence of CDOH was used to determine the equilibrium constant for the complex formation (see Experimental Section).[8]

Discussion

The Reaction Pathway. Our kinetic and isolation studies indicate that the observed acceleration of the hydrolysis of 1 and 2 occur through two reaction pathways. One involves the nucleophilic reaction of β-cyclodextrin anion (CDO^-) with the substrate, and the other does not involve covalent interaction between the β-cyclodextrin and the substrate.

We suggest that the mechanism of the reaction can be represented as shown in Scheme III.

The substrate 1-X-2,4-dinitrobenzene (S) undergoes a rapid reversible association with the β-cyclodextrin (CDOH) or with its partially ionized form (CDO^-). An alkoxide ion derived from the secondary hydroxyl group of CDOH reacts with a molecule of the substrate to form the product 3. On the other hand, the substrate complexed with CDOH (SCDOH) and with CDO^- ($SCDO^-$) reacts with

(8) Nakajima, T.; Sunagawa, M.; Hirohashi, T. *Chem. Pharm. Bull.* **1984**, *32*, 401.

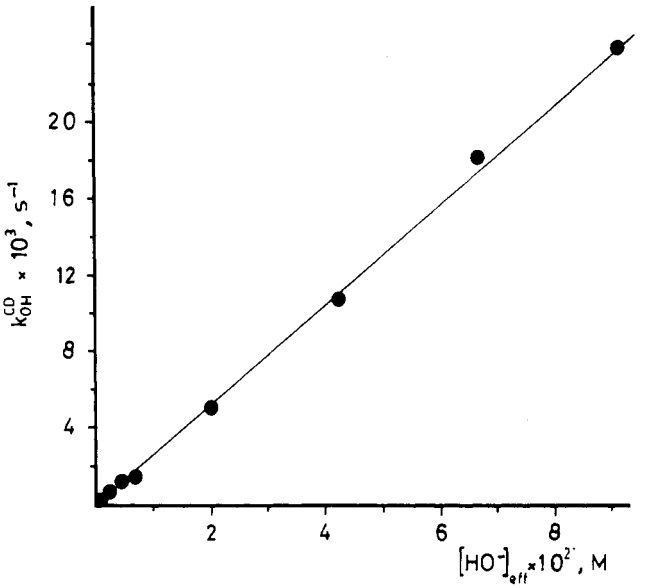


Figure 1. Dependence of k_{OH}^{CD} on the effective HO^- concentration for the reaction of 2,4-dinitrofluorobenzene in the presence of 0.01 M β-cyclodextrin. Solvent: dioxane–water (1/9 v/v). Ionic strength 0.2 M (NaCl as compensating electrolyte).

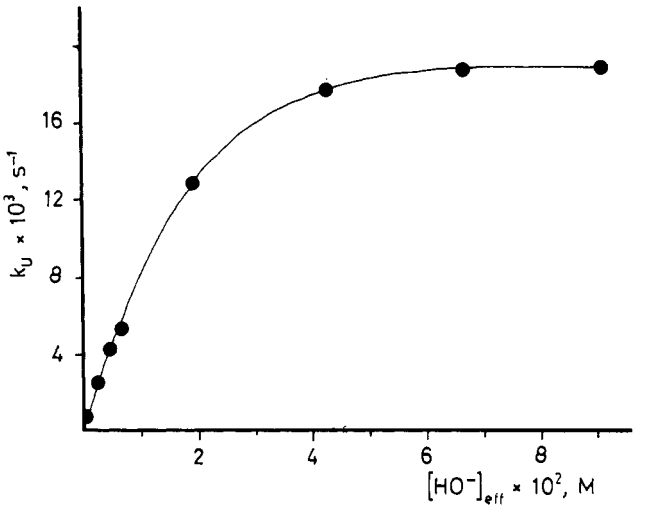
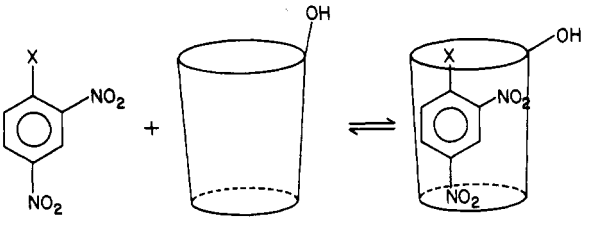


Figure 2. Dependence of k_u on the effective HO^- concentration for the reaction of 2,4-dinitrofluorobenzene in the presence of 0.01 M β-cyclodextrin. Solvent: dioxane–water (1/9 v/v). Ionic strength 0.2 M (NaCl as compensating electrolyte).

Scheme II



OH^- to give the hydrolysis product.

For the mechanism described in Scheme III k_u is given by eq 4

$$k_u = \frac{k_4 f(\mathrm{CDOH})_0 + k_5 K^-_{CD} f(\mathrm{CDOH})_0}{1 + K_{CD}(1 - f)(\mathrm{CDOH})_0 + K^-_{CD} f(\mathrm{CDOH})_0} \quad (4)$$

$$f = \frac{(OH^-)}{K_h + (OH^-)} \qquad K_h = \frac{(CDO^-)}{(\mathrm{CDOH})(OH^-)}$$

where k_4 is the rate constant for the reaction of CDO^- with

Table II. Pseudo-First-Order Rate Constants for the Hydrolysis of 2,4-Dinitrochlorobenzene as a Function of β-Cyclodextrin and NaOH Concentration[a]

no.	$(NaOH)_0$ M	$(HO^-)_{eff} \times 10^2$ [b] M	$(CDOH)_0 \times 10^3$ M	$k_{obsd} \times 10^5$ [c] seg^{-1}	$k_{OH}^{CD} \times 10^5$ [d] seg^{-1}	ratio[e]
1	0.14	13.1	10	3.41	4.25	2.1
2	0.17	16.1	10	3.99	4.88	2.0
3	0.20	19.0	10	4.55	5.32	1.8
4	0.050	4.27	10	1.36	1.22	1.9
5	0.067	5.91	10	1.73	1.60	1.8
6	0.083	7.48	10	2.04	1.78	1.6
7	0.10	9.15	10	2.37	2.22	1.6
8	0.10	9.96	0.50	1.90	1.90	1.3
9	0.10	9.94	0.70	1.94	1.96	1.3
10	0.10	9.91	1.0	1.90	1.95	1.3
11	0.10	9.87	1.5	1.98	1.94	1.3
12	0.10	9.83	2.0	2.04	2.06	1.4
13	0.10	9.72	3.0	2.12	2.29	1.6
14	0.10	9.66	4.0	2.30	2.30	1.6
15	0.10	9.49	6.0	2.34	2.34	1.6
16	0.10	9.32	8.0	2.39	2.10	1.5
17	0.50[f]	50.0	0.50	10.2	1.08	1.4
18	0.50[f]	49.9	0.70	10.7	1.15	1.5
19	0.50[f]	49.9	1.0	10.5	1.11	1.5
20	0.50[f]	49.8	2.0	10.4	1.09	1.4
21	0.50[f]	49.6	4.0	10.7	1.10	1.5
22	0.50[f]	49.4	6.0	11.0	1.16	1.6
23	0.50[f]	49.2	8.0	11.1	1.20	1.6
24	0.50[f]	49.0	10	11.2	1.24	1.7
25[g]	0.0010	0.062	10	42.6		1.0

[a] The solvent contains 10% v/v dioxane; ionic strength 0.2 M unless otherwise noted (NaCl as compensating electrolyte). Substrate concentration: $4.3–4.6 \times 10^{-5}$ M. [b] Calculated from the stoichiometric concentration of NaOH and the pK of CDOH = 12.2 taken from ref 2. [c] Calculated from a plot of ln $(A - A_\infty)$ vs. t during the first half-life. (A represents the absorbance of the solution at the wavelength maximum of 2,4-dinitrophenol at time t and A_∞ is calculated from the extinction coefficient of 2,4-dinitrophenol and the initial concentration of the substrate). [d] Calculated from computer fit of the data to eq 2 (see text). [e] Acceleration factor defined as the ratio of k_{OH}^{CD} to the rate constant for the hydrolysis in the absence of β-cyclodextrin. [f] Ionic strength 0.5 M. [g] The substrate is picryl chloride, and the solvent contains only 2% dioxane.

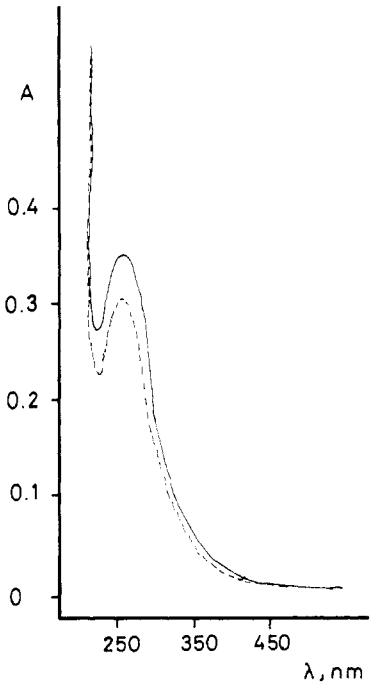
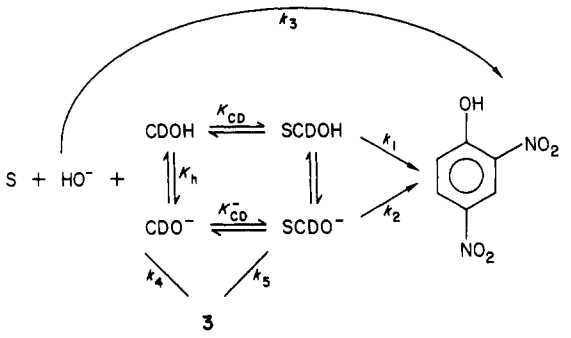


Figure 3. UV spectrum of 2,4-dinitrofluorobenzene in water and in water containing 0.01 M β-cyclodextrin. The blank solution for the latter contains 0.01 M β-cyclodextrin. Substrate concentration: 1.85×10^{-5} M.

the uncomplexed substrate, k_5 is the rate constant for the reaction of CDO^- with an included substrate molecule, K_{CD} is the equilibrium constant for the association of the substrate with CDOH, K^-_{CD} is the equilibrium constant for the association of the substrate with CDO^-, and f is the fraction of ionized cyclodextrin. We could determine K_{CD} using the partition function method[8] (see Experimental Section), but we could not use the same method to determine K^-_{CD} because CDO^- reacts with the substrate in the time needed to equilibrate the solutions.

Scheme III



Equation 4 can be rearranged into eq 5

$$\frac{1}{k_u} = \frac{K^-_{CD} - K_{CD}}{k_5 K^-_{CD} + k_4} + \frac{\dfrac{1}{(CDOH)_0} + K_{CD}}{k_5 K^-_{CD} + k_4}\left(\frac{1}{f}\right) \quad (5)$$

At constant $(CDOH)_0$, a plot (not shown) of $(k_u)^{-1}$ vs. $(f)^{-1}$ (Table I, no. 7–14) is linear and from the slope and intercept we can calculate $K^-_{CD} = 1.36 \times 10^3$ M^{-1} and $(k_5 K^-_{CD} + k_4) = 36$ M^{-1} s^{-1} (using $K_{CD} = 2 \times 10^3$ M^{-1}). Alternatively, $(k_u)^{-1}$ can be plotted vs. $(OH^-)^{-1}$ (Figure 4). This plot gives an excellent straight line, and assuming that $K_{CD} \approx K^-_{CD}$ from the ratio of slope and intercept we can calculate $K_h = 2.2 \times 10^{-2}$, which is in good agreement with literature values.

On the other hand, we cannot reproduce the data obtained at variable CDOH concentration and constant f using the values calculated above. This fact may indicate that this system is even more complicated than shown in Scheme I, and probably more than one type of complex is formed. Thus, the values K^-_{CD} and $k_5 K^-_{CD} + k_4$ calcu-

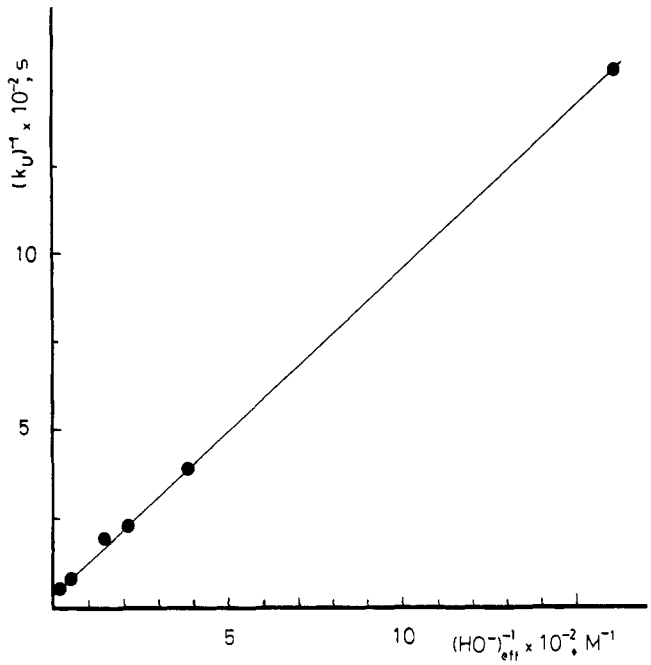


Figure 4. Plot of k_u^{-1} vs. the inverse of the effective concentration of HO^- for the reaction of 2,4-dinitrofluorobenzene in the presence of 0.01 M β-cyclodextrin.

lated above should be taken with caution.

For the reaction forming 2,4-dinitrophenol the observed pseudo-first-order rate constant k_{OH}^{CD} is given by eq 6. Since $K_{CD} \approx K^-_{CD}$; eq 6 can be simplified and rearranged into eq 7.

$$k_{OH}^{CD} = \frac{[k_1K_{CD}(1-f) + k_2K^-_{CD}f](CDOH)_0(OH^-) + k_3(OH^-)}{1 + (CDOH)_0[(K_{CD} - K^-_{CD})f + K_{CD}]} \quad (6)$$

$$\frac{k_{OH}^{CD}}{(OH^-)}[1 + K_{CD}(CDOH)_0] = [k_1K_{CD}(1-f) + k_2K^-_{CD}f](CDOH)_0 + k_3 \quad (7)$$

If $k_1 \approx k_2$ (see below), the slope of a plot of the left hand side of eq 7 vs. $[CDOH]_0$ gives $k_1K_{CD} = 554$ M^{-2} s^{-1} and hence $k_1 = 0.277$ M^{-1} s^{-1}. On the other hand, when the value of k_{OH}^{CD} obtained at constant CDOH concentration and variable OH^- concentration is plotted vs. OH^- concentration, a straight line is obtained (Figure 1). Since under the conditions of these experiments $K_{CD}(CDOH)_0 \gg 1$, the stright line of Figure 1 indicates that $k_1 \approx k_2$; thus eq 6 simplifies to eq 8. Then, from the slope of Figure 1, k_1 can be obtained, and this value is 0.268 M^{-1} s^{-1}. This value agrees with that calculated above with data obtained under different conditions.

$$k_{OH}^{CD} = \left[k_1 + \frac{k_3}{K_{CD}(CDOH)_0}\right](OH^-) \quad (8)$$

For the reactions of **2** we could only determine k_{OH}^{CD} from the computer fit of the experimental data. Under all conditions this value is higher than the k_3 value obtained for the reaction in the absence of CDOH. Since $K_{CD} = 4 \times 10^4$ M^{-1}, there is little variation of k_{OH}^{CD} with $(CDOH)_0$ concentration, and the rate coefficients for the elemental steps in Scheme III cannot be obtained, but the values of k_{OH}^{CD} at the higher concentration of CDOH should represent the rate of k_1 and k_2 steps (Scheme III). This value is 2 times higher than the value of k_3 determined independently in a solution without cyclodextrin which indicates that the effective rate of reaction within the cavity is twice as high as the reaction in the bulk solution.

The increase in rate of hydrolysis of the complexed substrates when compared with their uncomplexed counterparts indicates stabilization of the transition state for the reaction that occurs in the cavity. This stabilization is similar to that obtained when the rate of hydrolysis of a substrate such as 2,4-dinitroanisole is compared in 10% and 60% dioxane–water solution namely 8.2×10^{-4} M^{-1} s^{-1} and 1.59×10^{-3} M^{-1} s^{-1}, respectively.[9,10]

It has been suggested that the polarity of the cavity of CDOH is similar to that of dioxane.[11] Thus, the increase in rate in the hydrolysis of **1** and **2** may represent a microsolvent effect. The transition state for these reactions is a delocalized anion which can be better stabilized by the cavity of CDOH than the substrate itself. This conclusion can be inferred from the fact that the binding constant of CDOH to *p*-nitrophenoxide is higher than that to *p*-nitrophenol.[12]

Conclusions

We found that 1-X-2,4-dinitrobenzenes (X = Cl and F) are included into the cavity of β-cyclodextrin. As a result of the interaction the rate of consumption of both substrates increases. There are two mechanisms of catalysis. One involves the nucleophilic reaction of ionized cyclodextrin with the substrate, probably intramolecularly, to form a 2,4-dinitrophenylcycloheptaamylose intermediate which then further react in the reaction media forming 2,4-dinitrophenol. In the case of the reaction of 1-chloro-2,4-dinitrobenzene this mechanism represents true catalysis, since the hydrolysis of the intermediate is faster than its formation. On the other hand, in the reaction of 1-fluoro-2,4-dinitrobenzene this mechanism catalyzes the consumption of the substrate but not the formation of 2,4-dinitrophenol, since the hydrolysis of the intermediate is slow compared with the hydrolysis of the substrate itself.

The fact that one of the HO groups of β-cyclodextrin reacts with 1-fluoro-2,4-dinitrobenzene is remarkable[13] and probably means that the intramolecular reaction is favored by an appropriate orientation of the substrate in the cavity of the β-cyclodextrin.

The other mechanism of catalysis involves the hydrolysis of the complexed substrates and occurs through an estabilization of the transition state by a microsolvent effect.

Experimental Methods

Aqueous solutions were made up with twice-distilled water and reagent grade chemicals. Dioxane was purified by the Fieser[14] method.

β-Cyclodextrin was purchased from Sigma and used as received. Its purity was checked by descendent paper chromatography and thin-layer chromatography. 2,4-Dinitrofluorobenzene was distilled under vacuum, and 2,4-dinitrochlorobenzene was recrystallized from ethanol.

Reactions Kinetics. The hydrolysis of 2,4-dinitrochloro- and 2,4-dinitrofluorobenzene in alkaline solution was studied spectrophotometrically by using a Beckman 24 spectrophotometer with a thermostated cell compartment. The general experimental techniques have been described.[15]

(9) Bunnett, J. F.; Bernasconi, C. F. *J. Am. Chem. Soc.* **1965**, *87*, 5209.
(10) Bernasconi, C. F.; de Rossi, R. H.; Schmid, P. *J. Am. Chem. Soc.* **1977**, *99*, 4090.
(11) Hamai, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2721.
(12) Lin, S.-F.; Connors, K. A. *J. Pharm. Sci.* **1983**, *72*, 1333.
(13) Although primary alcohols react very well with aromatic compounds forming the corresponding phenyl–alkyl ethers, secondary alcohols lead mainly to reduction products. See, for instance: Prato, M.; Quintily, U.; Salvagno, S.; Scorrano, G. *Gazz. Chim. Ital.* **1984**, *144*, 413 and references cited therein.
(14) Fieser, L. F. *Experiments in Organic Chemistry*, 2nd ed.; D. R. Heath: Boston, Massachusetts, 1941; p 360.

The appearance of 2,4-dinitrophenol was measured at the wavelength of maximum absorption (368 nm).

Gel Filtration Chromatography. In order to effect a separation of 2,4-dinitrophenylcycloheptaamylose and other reaction products the following experiments were carried out.

β-Cyclodextrin (0.101 g, 8.92×10^{-5} mol) was dissolved in 90 mL of NaOH (10^{-3} M), and 2,4-dinitrofluorobenzene (0.0166 g, 8.92×10^{-5} mol) in 0.96 mL of dioxane was added.

The reaction mixture was stirred for 90 min, brought to pH 6–7 with a few drops of 0.1 M hydrochloric acid, and filtered to remove undissolved material. A 2.0-mL aliquot of the resulting solution was chromatographed by using a 1.5 × 28 cm column of Sephadex G-10 gel (Sigma).

The column was developed by eluting with distilled water. Consecutive 0.5-mL fractions were tested for the presence of cycloheptaamylose by thin-layer chromatography on silica gel using acetic acid/chloroform/water (80:10:10) as solvent.

Cycloheptaamylose was found to be present from the 6 to the 12–14 fractions taken after passage of the void volume, consistent with the molecular exclusion limits of Sephadex G-10. The 2,4-dinitrophenol was eluted after passing about 15 mL of water and the unreacted 2,4-dinitrofluorobenzene after about 30 mL of water. It is interesting to note that the 2,4-dinitrofluorobenzene is selectively retained by the Sephadex gel.

The ultraviolet absorption spectra of fractions 6–12 showed λ_{max} at 265 and 305 nm and were practically identical with the spectrum of 2,4-dinitroanisole. The thin-layer chromatography of these samples showed two compounds with R_f 0.22 and 0.38. The first one coincides with that of β-cyclodextrin.

A similar experiment was carried out by using 2,4-dinitrochlorobenzene, but in this case the reaction time was 33 h,[16] and the concentration of the solution contained 1×10^{-4} M 2,4-dinitrochlorobenzene, 0.01 M β-cyclodextrin, and 2.10^{-2} M NaOH.

A small amount of a compound having the same UV spectrum as that isolated from the reaction of 2,4-dinitrofluorobenzene appeared in fractions 7 and 8.

Equilibrium Constant for Complex Formation. To determine the equilibrium constant for complex formation between our substrates and CDOH, we used the partition coefficient method.[8] A solution prepared by dissolution of 2.47 mmol of 1 or 2 in 25 mL of benzene was mixed with 25 mL of water–dioxane (9:1 v/v) and stirred for 24 h. Then the two phases were separated by centrifugation for about 10 min, and 4 mL of the aqueous phase was withdrawn and diluted with NaOH (2.5 M) to hydrolyze the substrate. After the reaction was complete, the concentration of 2,4-dinitrophenol was determined by measuring its absorbance. The amount formed is equivalent to the amount of substrate dissolved in the water layer.

The ratio of concentration of the substrate in benzene (S_B) and in water (S_W) give the distribution constants (eq 9) 1.54×10^{-3} and 3.47×10^{-3} for 2,4-dinitrochlorobenzene and -fluorobenzene, respectively. The same determination was carried out at two

$$K_d = \frac{S_W}{S_B} \tag{9}$$

other initial concentrations in the benzene layer. The values of K_d obtained were independent of the concentration in the benzene layer within experimental error and also of the ratio of volumes of benzene and water.

The same determination was done but now by using a solution of 10^{-3} M β-cyclodextrin. The apparent equilibrium constant for complex formation was calculated from eq 10

$$K_{CD} = \frac{S_T - K_d(S_B)}{[(CDOH)_0 - S_T + K_d(S_B)]\, K_d(S_B)} \tag{10}$$

where S_T represents the total concentration of substrate in the water–dioxane–cyclodextrin solution, S_B is the concentration of the substrate in the benzene solution, and CDOH is the concentration of β-cyclodextrin in the water solution.

The concentration of β-cyclodextrin in water solution was determined by the phenol–sulfuric acid method,[17] and the value determined always coincides with the analytical concentration.

The value of K_{CD} thus determined was strongly dependent on the concentration of the substrate in the benzene layer and consequently in the water layer. As the concentration in the benzene layer increases K_{CD} decreases. For this reason, in our calculations we used the value of K_{CD} obtained for the lowest concentrations that give measurable amounts of substrate in the water layer, namely 4×10^4 M^{-1} and 2×10^3 M^{-1} for 2,4-dinitrochlorobenzene and -fluorobenzene, respectively.

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(16) This reaction time was chosen after calculating the time at which the concentration of product U in Scheme I should be maximum by using $k_{OH}^{CD} = 1.5 \times 10^{-4}$ M^{-1} s^{-1}, $k_u = 1.7 \times 10^{-3}$ M^{-1} s^{-1}; and $k_H = 4 \times 10^{-4}$ M^{-1} s^{-1}.

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Flash Vacuum Thermolysis of 5,6,8,9-Tetrahydro-4′-methylenespiro[7*H*-benzocycloheptene-7,1′-cyclohexa-2′,5′-diene]. The Intermediate Formation of [3,2]Orthoparacyclophane

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Flash vacuum thermolysis (FVT) of 5,6,8,9-tetrahydro-4′-methylenespiro[7*H*-benzocycloheptene-7,1′-cyclohexa-2′,5′-diene] (**2a**) at 520–650 °C yielded isomeric products **10** (26%), **12a** (14%), and **19** (3%) and 2,2′-dimethyldibenzyl (**17**, 22%). The formation of these products from the primary intermediate, the diradical **3a**, is discussed. It is concluded that **17** and **19** are formed via the intermediate [3,2]orthoparacyclophane (**1a**) which is unstable under FVT conditions. Attempts to investigate the regioisomer **2b** of **2a** were thwarted by the high reactivity of **2b** even at room temperature. FVT of **4a**, the 4′-keto precursor of **2a**, yielded **31** (60%); FVT of **4b** gave **17** (80%) and *p*-hydroxystyrene (**30**, 3%). In the thermolysis of **4**, cyclophanes are probably not involved.

In connection with our studies on the synthesis of short-bridged [*n*]para- and [*n*]metacyclophanes, we have reported that [8]- and [7]paracyclophane can be obtained by flash vacuum thermolysis (FVT) of methylenespiro-

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