

# Nucleophilic Displacements upon Phenyl Esters in Which the Direct Relationship between Basicity of the Leaving Group and Rate Is Determined by Ground State Conformations. A Question of Concerted Catalysis in the Hydrolysis of Hexachlorophene Esters

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**Abstract:** The log of the rate constants ( $\log k_{\text{rate}}$ ) for specific acid and specific base catalyzed hydrolysis, aminolysis, and intramolecular carboxyl anion nucleophilic catalysis of hydrolysis of the hexachlorophene esters I-V is linearly related to the  $\text{p}K_{\text{a}}$  values of the conjugate acids of the leaving phenolate moieties ( $\log k_{\text{rate}} = -\alpha \text{p}K_{\text{a}} + C$ ). The values of  $\alpha$  are *ca.* 1.0 for specific acid and base catalyzed hydrolysis and *ca.* 0.2 for aminolysis and carboxyl anion catalyzed hydrolysis. Thus, sensitivity to the basicity of the leaving group is great ( $\alpha \equiv 1.0$ ) for those reactions in which departure is not rate limiting but minimal ( $\alpha \equiv 0.2$ ) for those reactions in which departure is rate limiting. The direct relationship between leaving ability and rate must, therefore, be dependent upon a third factor which controls both. This factor is suggested to be the like ground state conformations of esters and phenols. The conformations allowing maximal internal hydrogen bonding in phenol (VII and IX) which provide for a  $\Delta \text{p}K_{\text{a}}$  of 5 also provide for minimal and maximal steric hindrance to approach of nucleophile to the ester bond. The hydrolysis of hexachlorophene monosuccinate (III), characterized by a "bell shaped"  $\text{pH}-\log k_{\text{rate}}$  profile, does not, as previously claimed, involve a push-pull catalytic mechanism consisting of carboxyl anion nucleophilic attack plus general acid catalysis by the phenolic group (XIII). Thus, methylation of the phenolic group of III to provide IV decreases the rate of carboxyl anion attack by but 3.2-fold. This is due to steric hindrance by the methyl substituent. Much larger steric effects accompanying methylation of the phenolic group are seen on comparing the rate constants for specific acid catalyzed hydrolysis of III *vs.* IV ( $k_{\text{rel}} : 1/29$ ) and the corresponding acetyl esters I *vs.* II ( $k_{\text{rel}} : 1/749$ ).

Based on an experimental reevaluation of reported examples, Maugh and Bruice in 1971 concluded that there were no known examples of concerted intramolecular bifunctional catalysis of ester hydrolysis (*i.e.*, concerted general acid and general base or general acid and nucleophilic catalysis).<sup>1</sup> In a most interesting study of the hydrolysis of hexachlorophene esters Higuchi, *et al.*,<sup>2</sup> reported a *ca.*  $1.5 \times 10^7$ -fold differential in the rate constants for hydrolysis of the monosuccinate ester of hexachlorophene (III) as compared to the diacetyl ester V. They attributed the much greater rate constant for III to concerted intramolecular nucleophilic (succ-COO<sup>-</sup>) and general acid (phenolic-OH) catalysis. If confirmed as a "push-pull" mechanism this finding would have profound implications in acid-base catalysis, particularly in regard to enzyme catalysis.

In the investigation reported herein the various pathways for hydrolysis as well as for aminolysis and trifluoroethoxide transesterification of a number of hexachlorophene esters are reported. From a comparison of the rate constants for carboxyl anion participation in the hydrolysis of III and ester IV it becomes obvious that there is no "push-pull" mechanism in the hydrolysis of III. The log of the values of the various rate constants (specific acid, specific base, and intramolecular carboxyl anion catalyzed hydrolysis and aminolysis) are found to be linearly related to the  $\text{p}K_{\text{a}}$  values of the conjugate acids of the hexachlorophene leaving groups. This establishes a direct relationship between the  $\Delta F^{\ddagger}$

values for the nucleophilic displacements on the ester species ( $\Delta F^{\ddagger}_{\text{nuc}}$ ) and for water attack ( $\Delta F^{\ddagger}_{\text{OH}}$ ) on the dissociable proton of the conjugate acids of the leaving groups (*i.e.*,  $\Delta \Delta F^{\ddagger}_{\text{nuc}} = -\alpha \Delta \Delta F^{\ddagger}_{\text{OH}}$ ). On the basis of arguments that include the fact that  $\alpha$  is *ca.* 1.0 for specific base and specific acid catalysis, where the rate-limiting step is solely attack and partially attack, respectively, and *ca.* 0.2 for intramolecular carboxyl anion catalysis and aminolysis, where the rate-limiting step is departure, it is concluded that the relationship of  $\Delta F^{\ddagger}_{\text{nuc}}$  to  $\Delta F^{\ddagger}_{\text{HO}}$  reflects a mutual dependence not on the leaving ability of the phenolate moiety but on the steric conformations of the substrates. Thus, the similar steric conformations of the esters and phenols control the rate constants for nucleophilic attack both upon the ester carbonyl groups and upon the dissociable proton of the phenols.

## Experimental Section

**Apparatus.** All spectrophotometric kinetic measurements were made on either a Gilford Model 2000 spectrometer equipped with four thermospacers through which water at  $30 \pm 0.1^\circ$  was circulated or a spectrophotometric titration apparatus<sup>3</sup> designed around the Cary 15 spectrophotometer and Radiometer autotitrator through which water was circulated at  $30 \pm 0.1^\circ$ . pH measurements ( $30 \pm 0.1^\circ$ ) were taken with a Radiometer Model 22 pH meter equipped with a Model 630 scale expander or pH meter Type PHM 26 and a Radiometer G. K. 2021C combined glass calomel electrode. Correction of pH meter readings to pH was accomplished as described by Bates, *et al.*,<sup>4</sup> for aqueous methanol solutions. Infrared spectra were recorded in potassium bromide disks using a Perkin-Elmer 137 sodium chloride spectrophotometer.

(1) T. Maugh II and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3237 (1971).

(2) T. Higuchi, H. Takechi, I. H. Pitman, and H. L. Fung, *J. Amer. Chem. Soc.*, **93**, 539 (1971).

(3) J. R. Maley and T. C. Bruice, *Anal. Biochem.*, **34**, 275 (1970).

(4) R. G. Bates, M. Paaabo, and R. A. Robinson, *J. Phys. Chem.*, **67**, 1833 (1963).

Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as internal standard.

**Materials.** Reagent grade potassium chloride, potassium acetate, acetic acid, sodium borate, and potassium phosphate monobasic were used without further purification. Aqueous methanol solvent (50/50 by weight) was prepared by mixing deionized double glass distilled water and distilled methanol (Mallinckrodt). Ionic strength was kept at  $\mu = 0.25$  with potassium chloride. Spectro-quality dioxane (Mallinckrodt) was refluxed over sodium metal for a minimum of 24 hr and then distilled through a 4-ft column packed with glass helices. *n*-Propylamine (Eastman, bp 48°) and triethylamine (Mallinckrodt, bp 89°) were distilled at atmospheric pressure and benzylamine (Eastman) and 2-methoxyethylamine (Aldrich) were distilled under reduced pressure. Glycine amide hydrochloride (Aldrich) and hydrazine monohydrochloride (Eastman) were recrystallized from aqueous ethanol. Imidazole (Aldrich) was recrystallized twice from benzene. Glycylglycine (Aldrich) and trifluoroethanol (Aldrich) were used without further purification.

**Hexachlorophene Monoacetate (I).** Hexachlorophene (Pfaltz and Bauer), 20.4 g (0.05 mol), was dissolved in 250 ml of dried and freshly distilled pyridine. Acetyl chloride, 4.0 g (0.05 mol), was then added dropwise to the solution with vigorous stirring. The addition was continued for 60 min and then after the exothermic reaction subsided, the reaction mixture was refluxed for an additional 4 hr and left overnight at room temperature. Pyridine was removed under reduced pressure. The residue was washed twice with cold water and recrystallized from benzene-*n*-hexane (67/33 by volume). I had mp 148.5–149.5° uncor; strong  $\nu_{C=O}$  1745  $cm^{-1}$ ; nmr singlets at  $\delta$  7.6 (1 H), 7.5 (1 H), 4.5 (2 H), 2.2 ppm (3 H). *Anal.* Calcd for  $C_{17}H_{10}O_3Cl_6$ : C, 40.13, H, 1.78; Cl, 47.38. Found: C, 40.23; H, 2.12; Cl, 47.22.

***O*-Methylhexachlorophene Acetate (II).** Hexachlorophenemomethyl ether was prepared by heating methyl iodide, 14.2 g (0.10 mol), and hexachlorophene, 40.7 g (0.10 mol), under reflux in 500 ml of acetone and potassium bicarbonate, 10.0 g (0.10 mol), for 6 hr. Hexachlorophene monomethyl ether melted at 139.5°; nmr broad singlet at  $\delta$  7.4 (2 H), singlet at 4.5 (2 H) and 3.7 ppm (3 H). II was prepared from *O*-methylhexachlorophene and acetyl chloride in the same manner as compound I. II had mp 134.0°; strong  $\nu_{C=O}$  1750  $cm^{-1}$ ; nmr singlets at  $\delta$  7.50 (1 H), 7.45 (1 H), 4.4 (2 H), 3.5 (3 H), 2.1 ppm (3 H). *Anal.* Calcd for  $C_{18}H_{10}O_3Cl_6$ : C, 41.68; H, 2.18; Cl, 45.94. Found: C, 41.65; H, 2.28; Cl, 45.82.

**Sodium Salt of Hexachlorophene Succinate (III).** Hexachlorophene was recrystallized from benzene-*n*-hexane (67/33 by volume) and thoroughly dried under vacuum over  $P_2O_5$ . Succinic anhydride was refluxed for 3 hr in acetic anhydride, then crystallized by cooling and recrystallized from the same solvent, and dried at 60° under a vacuum. Hexachlorophene, 20.4 g (0.05 mol), was dissolved with stirring and heating in 250 ml of dioxane (dried by refluxing and distillation over sodium metal), sodium shot, 1.15 g (0.05 mol), was added with stirring, and the flask was kept warmed under anhydrous conditions. After 5 hr, succinic anhydride, 0.5 g (0.05 mol), was dissolved in 15 ml of dioxane and added dropwise to the reaction solution. Heating was discontinued and the solution was stirred at room temperature overnight. The reaction mixture was concentrated to one-third volume under vacuum and was cooled to 10° to yield a pale-yellow precipitate which was collected by filtration, thoroughly washed with sodium dried ether, and stored under vacuum. The powder exhibited ir absorption at 1745  $cm^{-1}$  and no absorbance due to succinic anhydride (1865 and 1782  $cm^{-1}$ ); nmr singlets at  $\delta$  7.6 (1 H), 7.5 (1 H), 4.5 ppm (2 H), double triplet centered at 2.8 ppm (4 H). Assay for per cent of hexachlorophene in the ester molecule was performed by hydrolysis at pH 12.0 and comparison of the absorbance at  $t_{\infty}$  to a Beer's law plot at 300 nm constructed from the absorbance of standard hexachlorophene solutions. The analytical results indicated that the ester contained ca. 20% excess of unreacted hexachlorophene. Attempts to purify the sodium salt proved fruitless.

**Sodium Salt of *O*-Methylhexachlorophene Succinate (IV).** Hexachlorophene monomethyl ether and succinic anhydride were allowed to react in the presence of sodium metal in dioxane in the manner employed for the preparation of III. The ir spectrum of the product exhibited absorbance at 1770  $cm^{-1}$  attributable to an ester carbonyl but no absorbance at 1865 and 1782  $cm^{-1}$  attributable to succinic anhydride. The nmr spectrum exhibited singlets at  $\delta$  7.40 (1 H), 7.45 (1 H), 4.4 (2 H), 3.6 ppm (3 H), and a double triplet centered at  $\delta$  2.8 ppm (4 H). The salt of IV obtained contained ca.

25% of unreacted hexachlorophene monomethyl ether by spectral analysis (see preparation of III).

**Hexachlorophene Diacetate (V).** Hexachlorophene diacetate was prepared by adding 10.0 g (0.125 mol) of acetyl chloride to 20.4 g (0.05 mol) of hexachlorophene in 500 ml of pyridine. After removing pyridine under vacuum the solid was recrystallized from benzene-*n*-hexane (67/33 by volume). V had mp 171.5–172° uncor; strong  $\nu_{C=O}$  1770  $cm^{-1}$ ; nmr singlets at  $\delta$  7.4 (2 H), 4.3 (2 H), 2.1 ppm (6 H). *Anal.* Calcd for  $C_{17}H_{10}O_4Cl_6$ : C, 41.59; H, 2.05; Cl, 43.32. Found: C, 41.46; H, 2.06; Cl, 43.52.

**Kinetic Measurements.** All kinetic studies were carried out in  $CH_3OH-H_2O$  (50/50 by weight) at  $\mu = 0.25$  (with KCl), at a temperature of  $30 \pm 0.1^\circ$ , and followed spectrophotometrically. All solvolytic reactions were followed at constant pH and when buffers were employed their concentration far exceeded that of ester so that the disappearance of the ester and the appearance of the phenolic products occurred at the same rate and in a manner described by pseudo-first-order kinetics. When lyate species rate constants were obtained from intercepts of buffer dilution plots, these pseudo-first-order rate constants were found to coincide with the value obtained by use of a spectrophotometric pH stat. The pH values of all solutions were determined before and just after the completion of the reaction and rates were rejected if the pH changed by more than 0.02 pH unit.

Unless noted otherwise all reactions were initiated by addition of ester in dioxane to the buffered or pH-statted aqueous methanol solutions to give final concentrations of ester and dioxane of  $10^{-5}$ – $10^{-6}$  *M* and ca. 1%, respectively. Usually dioxane was used as the organic solvent for stock solutions but its replacement by acetonitrile did not significantly affect the measured rates. Because of the small optical density change on hydrolysis of esters III and IV between pH 1.0 and 5.0, solutions of  $1.0$ – $2.0 \times 10^{-4}$  *M* were required. Due to the low solubility of the sodium salts of these esters in dioxane (or acetonitrile), freshly prepared methanol stock solutions were also employed. In this case, the change of solvent and concentration did not significantly affect the measured rate.

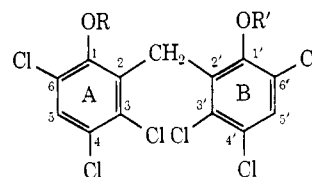
The wavelengths used to follow the reaction rates spectrophotometrically are as follows: 300 nm for ester I and ester III, and 315 nm for ester II and IV [290 nm was also used for ester I (pH 1.0–5.0)]. Reaction rates were computer calculated *via* least-squares analysis of plots of  $\ln(OD_{\infty} - OD_0)/(OD_{\infty} - OD_t)$  vs. *t*.

$pK_a$  values of amines were determined titrimetrically. The conditions employed were those of kinetic measurements ( $30 \pm 0.1^\circ$ ,  $CH_3OH-H_2O$  50/50 by weight,  $\mu = 0.25$  with KCl).

**Deuterium solvent kinetic isotope effects** were investigated in  $CH_3OD-D_2O$  in place of  $CH_3OH-H_2O$ .  $pD$  correction was carried out as follows. Standard solutions of  $6.52 \times 10^{-3}$  *N* DCl in  $CH_3OD-D_2O$  (50/50 by weight, prepared from concentrated aqueous HCl and 99.7%  $D_2O$  and 99%  $CH_3OD$ ) and HCl in  $CH_3OH-H_2O$  (50/50 by weight) were prepared. pH measurements were done in the same manner described before at  $30^\circ$  and  $\Delta pD$  (numerical correction which must be added to the meter reading to obtain real  $pD$ ) was found to be 0.37.

## Results

The hydrolysis of esters I–V has been investigated.



- I, R =  $CH_3C(=O)-$ ; R' = H-  
 II, R =  $CH_3C(=O)-$ ; R' =  $CH_3-$   
 III, R =  $HOC(=O)CH_2CH_2C(=O)-$ ; R' = H-  
 IV, R =  $HOC(=O)CH_2CH_2C(=O)-$ ; R' =  $CH_3-$   
 V, R = R' =  $CH_3C(=O)-$

Plots of the logarithms of the observed first-order hydrolytic rate constants ( $\log k_{obsd}$ ) vs. pH for hydrolysis of I–V [solvent  $CH_3OH-H_2O$  50/50 (w/w),  $30 \pm 0.1^\circ$ ,  $\mu = 0.25$  with KCl] are given in Figure 1. In the pH range 2.5–11.0, either an external buffer was employed and the appropriate lyate species first-order rate constants were obtained by extrapolation to zero buffer concentration or the pH was maintained by use of a

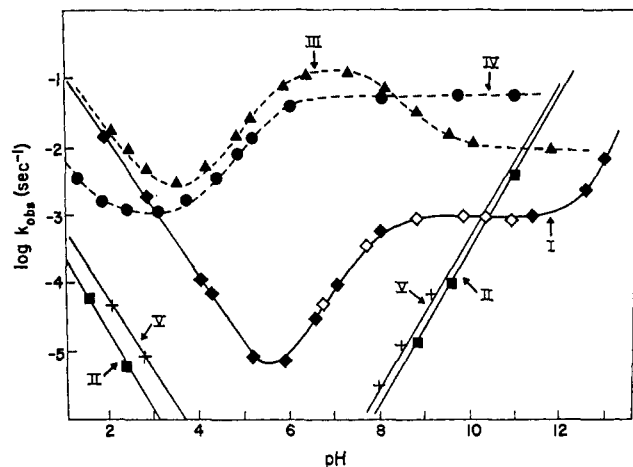


Figure 1. pH-log  $k_{\text{obsd}}$  profiles of the hydrolysis of hexachlorophene esters [30° in  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (50/50) by weight,  $\mu = 0.25$  with  $\text{KCl}$ ].

Table I. Values of Rate and Ionization Constants Utilized to Provide the Calculated Lines of Figure 1

Substrate	Kinetic expression	$\text{p}K_{\text{a}}$	Rate constant			
I	1	$\text{p}K_{\text{a}1} = 7.9$	$k_{\text{H}}^{\text{I}}$ $1.05 \text{ M}^{-1} \text{ sec}^{-1}$			
			$k_0^{\text{I}}$ $2.0 \times 10^{-6} \text{ sec}^{-1}$			
			$k_{\text{LO}}^{\text{Ia}}$ $2.02 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$			
			$k_{\text{LO}}^{\text{Ib}}$ $7.08 \text{ M}^{-1} \text{ sec}^{-1}$			
II	2		$k_{\text{H}}^{\text{II}}$ $1.41 \times 10^{-3} \text{ M}^{-1} \text{ sec}^{-1}$			
			$k_{\text{LO}}^{\text{II}}$ $1.42 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$			
			III	3	$\text{p}K_{\text{a}2} = 5.8$ $\text{p}K_{\text{a}3} = 8.2$	$k_{\text{H}}^{\text{III}}$ $1.15 \text{ M}^{-1} \text{ sec}^{-1}$
						$k_0^{\text{IIIa}}$ $1.78 \times 10^{-3} \text{ sec}^{-1}$
IV	4	$\text{p}K_{\text{a}4} = 5.7$	$k_0^{\text{IIIb}}$ $1.42 \times 10^{-1} \text{ sec}^{-1}$			
			$k_0^{\text{IIIc}}$ $7.08 \times 10^{-3} \text{ sec}^{-1}$			
			$k_{\text{H}}^{\text{IV}}$ $3.98 \times 10^{-2} \text{ M}^{-1} \text{ sec}^{-1}$			
			$k_0^{\text{IVa}}$ $7.08 \times 10^{-4} \text{ sec}^{-1}$			
V	5		$k_0^{\text{IVb}}$ $4.47 \times 10^{-2} \text{ sec}^{-1}$			
			$k_{\text{H}}^{\text{V}}$ $3.52 \times 10^{-3} \text{ M}^{-1} \text{ sec}^{-1}$			
			$k_{\text{LO}}^{\text{V}}$ $2.20 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$			

pH stat. Below pH 2.5 buffer capacity was maintained by hydronium ion and above pH 11 by hydroxide ion. Hydrolytic rate constants for IV were not altered when *O*-methylhexachlorophene was added to the kinetic solution at a concentration equal to the initial concentration of ester. The points on the plots of Figure 1 are experimental and the lines theoretical, generated from empirical eq 1-5 employing the constants of Table I. The  $k_{\text{H}}$ ,  $k_0$ , and  $k_{\text{LO}}$  rate constants of eq 1-5 pertain

$$k_{\text{obsd}}^{\text{I}} = \frac{k_{\text{H}}^{\text{I}} a_{\text{H}}^2}{a_{\text{H}} + K_{\text{a}1}} + \frac{k_0^{\text{I}} a_{\text{H}}}{a_{\text{H}} + K_{\text{a}1}} + \frac{k_{\text{LO}}^{\text{Ia}} a_{\text{H}} K_{\text{w}}}{(a_{\text{H}} + K_{\text{a}1}) a_{\text{H}}} + \frac{k_{\text{LO}}^{\text{Ib}} K_{\text{a}1} K_{\text{w}}}{(a_{\text{H}} + K_{\text{a}1}) a_{\text{H}}} \quad (1)$$

$$k_{\text{obsd}}^{\text{II}} = k_{\text{H}}^{\text{II}} a_{\text{H}} + k_{\text{LO}}^{\text{II}} \frac{K_{\text{w}}}{a_{\text{H}}} \quad (2)$$

$$k_{\text{obsd}}^{\text{III}} = \frac{k_{\text{H}}^{\text{III}} a_{\text{H}}^3 + k_0^{\text{IIIa}} a_{\text{H}}^2 + k_0^{\text{IIIb}} K_{\text{a}2} a_{\text{H}} + k_0^{\text{IIIc}} K_{\text{a}2} K_{\text{a}3}}{a_{\text{H}}^2 + K_{\text{a}2} a_{\text{H}} + K_{\text{a}2} K_{\text{a}3}} \quad (3)$$

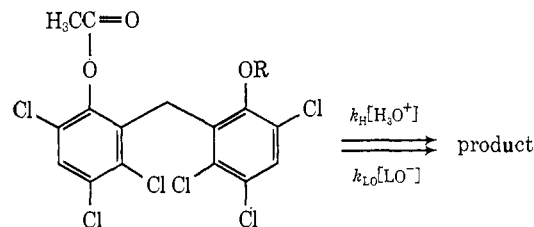
$$k_{\text{obsd}}^{\text{IV}} = \frac{k_{\text{H}}^{\text{IV}} a_{\text{H}}^2 + k_0^{\text{IVa}} a_{\text{H}} + k_0^{\text{IVb}} K_{\text{a}4}}{a_{\text{H}} + K_{\text{a}4}} \quad (4)$$

$$k_{\text{obsd}}^{\text{V}} = k_{\text{H}}^{\text{V}} a_{\text{H}} + k_{\text{LO}}^{\text{V}} \frac{K_{\text{w}}}{a_{\text{H}}} \quad (5)$$

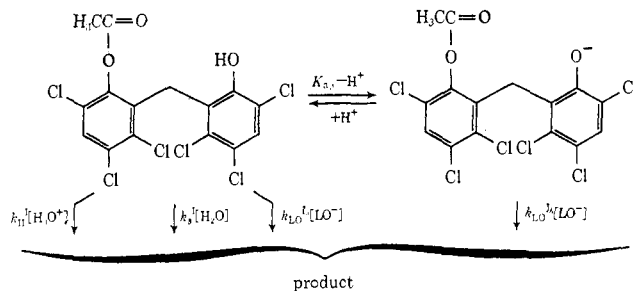
to specific acid catalysis, spontaneous and lyate anion solvolysis, respectively. In the calculation of the  $k_{\text{LO}}$  constants of Table I we have arbitrarily ignored the separate contribution of  $\text{HO}^-$  and  $\text{CH}_3\text{O}^-$  and have employed the value of 16.2 for  $K_{\text{w}}$  (reported as the dissociation constant of water in 50/50 by weight aqueous ethanol solution)<sup>5</sup> in the calculation of lyate anion concentration,  $[\text{LO}^-]$ . Considering the slight difference in temperature and the restricted pH range employed by Higuchi and coworkers,<sup>2</sup> the pH-log  $k_{\text{obsd}}$  profiles for the hydrolysis of I and II, as recorded in this and Higuchi's study coincide. The rate constant for alkaline hydrolysis of II, reported herein, is quite similar to that of hexachlorophene diacetate (V) reported by Higuchi<sup>2</sup> and reconfirmed by ourselves.

The least encumbered reaction pathways for solvolysis of I-V which are in accord with eq 1-5 are provided in Schemes I-IV. In Table I are listed the values

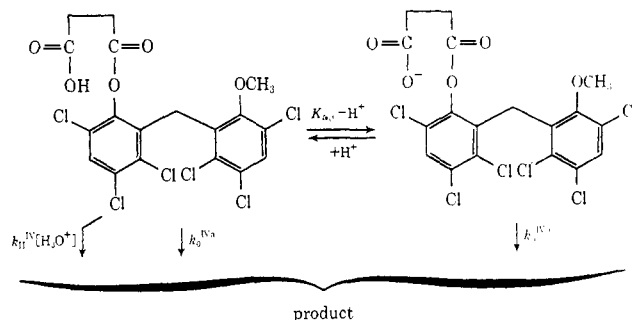
Scheme I. Esters II and V



Scheme II. Ester I



Scheme III. Ester IV



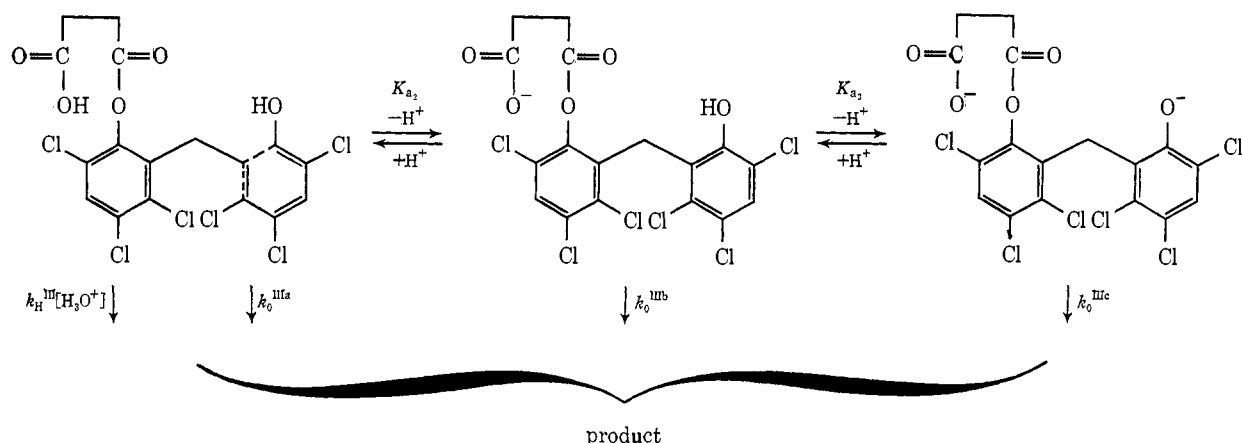
(5) E. M. Wooley, D. G. Hurkot, and L. G. Hepler, *J. Phys. Chem.* 74, 3908 (1970).

Table II. Second-Order Rate Constants for the Aminolysis of I and II

Amine	pK <sub>a</sub> <sup>a</sup>	pH region	Rate constant, M <sup>-1</sup> sec <sup>-1</sup>	k <sub>n</sub> <sup>I</sup> /k <sub>n</sub> <sup>II</sup>	k <sub>n</sub> <sup>I</sup> ⁻/k <sub>n</sub> <sup>II</sup>
<i>N</i> -Propylamine	10.11	9.56–11.16	k <sub>n</sub> <sup>I</sup> 1.45 × 10 <sup>-2</sup> k <sub>n</sub> <sup>II</sup> 3.30 × 10 <sup>-2</sup>		0.44
2-Methoxyethylamine	9.06	8.63–9.64	k <sub>n</sub> <sup>I</sup> 1.65 × 10 <sup>-2</sup> k <sub>n</sub> <sup>I</sup> ⁻ 4.32 × 10 <sup>-3</sup> k <sub>n</sub> <sup>II</sup> 6.27 × 10 <sup>-3</sup>	2.63	0.69
Benzylamine	8.85	8.51–9.41	k <sub>n</sub> <sup>I</sup> 1.08 × 10 <sup>-2</sup> k <sub>n</sub> <sup>I</sup> ⁻ 5.02 × 10 <sup>-3</sup> k <sub>n</sub> <sup>II</sup> 5.50 × 10 <sup>-3</sup>	1.96	0.91
Glycine amide	7.90	7.36–8.54	k <sub>n</sub> <sup>I</sup> 1.40 × 10 <sup>-3</sup> k <sub>n</sub> <sup>I</sup> ⁻ 8.0 × 10 <sup>-4</sup> k <sub>n</sub> <sup>II</sup> 9.0 × 10 <sup>-4</sup>	1.55	0.89
Hydrazine	7.94	7.34–9.44	k <sub>n</sub> <sup>I</sup> 4.40 × 10 <sup>-3</sup> k <sub>n</sub> <sup>I</sup> ⁻ 3.98 × 10 <sup>-3</sup> k <sub>n</sub> <sup>II</sup> 2.75 × 10 <sup>-3</sup>	1.60	1.45
Imidazole	6.76	6.10–7.07	k <sub>n</sub> <sup>I</sup> 1.90 × 10 <sup>-3</sup> k <sub>n</sub> <sup>II</sup> 2.02 × 10 <sup>-3</sup>	0.94	

<sup>a</sup> Determined in 50/50 (w/w) CH<sub>3</sub>OH–H<sub>2</sub>O at 30 ± 0.1°.

Scheme IV. Ester III



of the rate constants of eq 1–5 employed to fit the experimental values of  $k_{\text{obsd}}$  to the  $\log k_{\text{obsd}}$  vs. pH profiles of Figure 1. The deuterium solvent kinetic isotope effect for hydrolysis of I at the plateau in the alkaline pH range (pH = pD = 9.55 ± 0.03) is  $k_{\text{obsd}}^{\text{H}_2\text{O}}/k_{\text{obsd}}^{\text{D}_2\text{O}} = 8.91 \times 10^{-4} \text{ sec}^{-1}/8.38 \times 10^{-4} \text{ sec}^{-1} = 1.06$ .

Aminolysis of the monoacetates I and II was carried out employing the same solvent and temperature used for the hydrolytic reactions and under the pseudo-first-order condition of total amine (free base [N] and conjugate acid [NH]) in great excess of ester. The disappearance of ester in the presence of amine buffers was found to follow eq 6 where  $k$  is the apparent first-

$$-\frac{d[\text{ester}]}{dt} = (k + k'_n[\text{N}])[\text{ester}] \quad (6)$$

order rate of solvolysis at the pH employed and  $k'_n$  the apparent second-order rate constant for aminolysis. Values of  $k'_n$  were obtained from slopes of plots of  $(k_{\text{obsd}} - k)$  vs.  $[K_a/(K_a + a_H)][[N_T]]$  at constant pH. For II,  $k'_n$  is equal to the true second-order rate constant for reaction of amine with ester ( $k_n^{\text{II}}$ ). For I,  $k'_n$  was found to be dependent upon the hydrogen ion activity as shown in eq 7. The values of  $k_n^{\text{I}}$  and  $k_n^{\text{I}^-}$

$$k'_n = k_n^{\text{I}} \frac{a_H}{K_I + a_H} + k_n^{\text{I}^-} \frac{K_I}{K_I + a_H} \quad (7)$$

were obtained from the sigmoid plots of  $k_n$  vs. pH as the lower and upper plateau, respectively. The values of  $k_n$  for I and II are provided in Table II and the derived

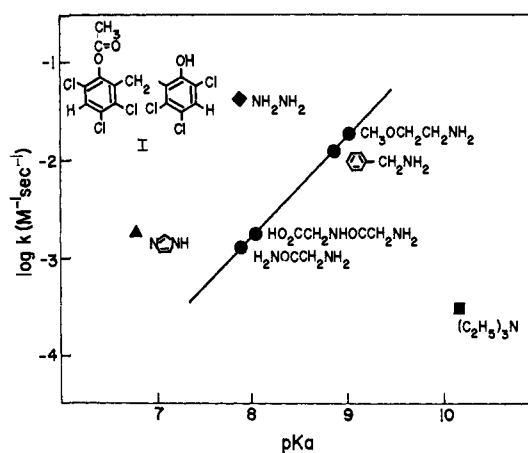


Figure 2. Plots of  $\log k_n^{\text{I}}$  vs. pK<sub>a</sub> for the reaction of amines with hexachlorophene monoacetate [30°, CH<sub>3</sub>OH–H<sub>2</sub>O (50/50) by weight,  $\mu = 0.25$  with KCl].

Brønsted plots are shown in Figures 2 and 3. The slopes of the Brønsted plots are 0.92 for I and 0.88 for II. The points for hydrazine ( $\alpha$  effect) and imidazole exhibit their usual positive deviation and triethylamine has the usual negative deviation from the best Brønsted line.<sup>6</sup> The magnitude of the  $\beta_{\text{Nuc}}$  values are normal for aminolysis of substituted phenyl acetates.<sup>7–9</sup> The

(6) T. C. Bruice, A. Donzel, R. W. Huffmann, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967).

(7) T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, **80**, 2265 (1958).

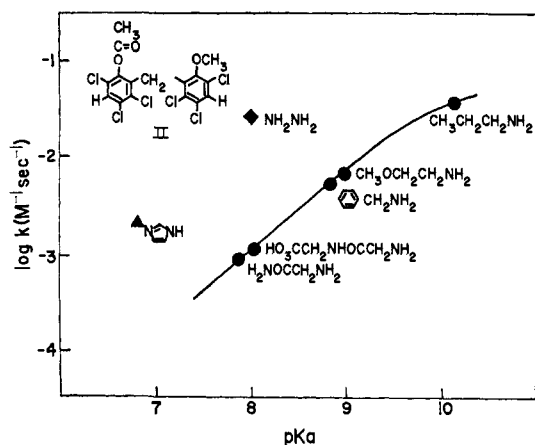


Figure 3. Plots of  $\log k_n^{11}$  vs.  $pK_a$  for the reaction of amines with *O*-methylhexachlorophene acetate [30°,  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (50/50) by weight,  $\mu = 0.25$  with KCl].

point for triethylamine most likely represents amine general base catalyzed assistance to  $\text{H}_2\text{O}$  attack.<sup>9</sup>

The dependence of the rate of ester disappearance upon trifluoroethanol concentration (pH 11.86 for I and 11.81 for II) is provided in Figure 4. Examination of these figures show that an increase in trifluoroethanol concentration increases the rate of disappearance of II but not of I. At pH 8.21 no increase in the rate of disappearance of I or II was noted with increasing concentration of trifluoroethanol. These results indicate that  $\text{CF}_3\text{CH}_2\text{O}^-$  is the reactive entity. In a previous study it was shown that  $\text{CF}_3\text{CH}_2\text{O}^-$  is present in sufficient concentration at pH 7 ( $\text{CF}_3\text{CH}_2\text{OH}$ ,  $pK_a = 12.36$ ) to be a most effective nucleophile toward *p*-nitrophenyl acetate.<sup>10</sup> Since the  $pK_a$  of  $\text{CF}_3\text{CH}_2\text{OH}$  in 50/50  $\text{H}_2\text{O}-\text{MeOH}$  (w/w) is not known, the second-order rate constant for reaction of I with  $\text{CF}_3\text{CH}_2\text{O}^-$  cannot be calculated. Nevertheless, a maximal ratio of  $k_{\text{CF}_3\text{CH}_2\text{O}^-}^{11}/k_{\text{H}_2\text{O}}^{11}$  may be calculated if it is assumed, due to experimental error, that a 5.0% increase in  $k_{\text{obsd}}$  over  $k$  is obtained for disappearance of I at the highest value of  $[\text{CF}_3\text{CH}_2\text{OH}]$  employed at pH 11.86. With this assumption, the ratio of the slopes of Figure 4 would be equal to *ca.* 54. This value is not very enlightening since it represents a minimum and could be orders of magnitude greater.

## Discussion

The rate constants for specific acid catalyzed hydrolysis of phenyl acetates have proved to be completely insensitive to the electronic nature of the leaving phenol.<sup>11</sup> In fact, Ingold's<sup>12</sup> recognition of the insensitivity of specific acid catalysis ( $k_H$ ) of ester hydrolysis electronic effects led to Taft's<sup>13</sup> suggestion that  $\log k_H$  values be employed as steric constants for substituent groups. Examination of the specific acid rate constants for the esters of this study reveals that the 1' substituent

(8) W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **82**, 1778 (1960).

(9) P. Y. Bruice and T. C. Bruice, *J. Amer. Chem. Soc.*, in press.

(10) T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962).

(11) A. J. Kirby in "Comprehensive Chemical Kinetics," C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, New York, N. Y., 1972, Chapter 2.

(12) C. K. Ingold, *J. Chem. Soc.*, 1032 (1930).

(13) R. W. Taft, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, London, 1956, p 556.

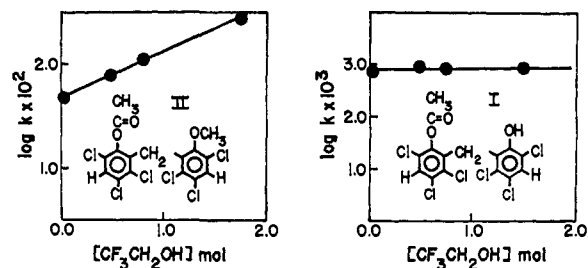


Figure 4. Plots of  $k_{\text{obsd}}$  vs. concentration of 2,2,2-trifluoroethanol for the solvolysis of hexachlorophene monoacetate and *o*-methylhexachlorophene acetate [pH 11.86 for I, 11.81 for II, 30°,  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (50/50) by weight,  $\mu = 0.25$  with KCl].

of the B ring has a profound influence on their values (Table I). It logically follows that the relative values of these rate constants (Table III) are determined by

Table III. Relative Values of  $k_H$

Constant	Rel to $k_H^1$
$k_H^1$	1.0
$k_H^{11}$	1/748
$k_H^{111}$	1/0.91
$k_H^{1V}$	1/26.5
$k_H^V$	1/299

the steric demand of the substituent at the 1' position of ring B. This requires that substituents on the 1 and 1' positions of rings A and B approach each other (VIB) and/or that an increase in steric demand of the 1' substituent brings about a conformation change in which the 6'-chloro substituent is brought into closer proximity to the 1-ester substituent (VIC). From Table III it may be seen that replacement of the phenolic proton on ring B by a methyl group decreases the rate of acid-catalyzed hydrolysis by 748-fold for the acetyl ester and by 29-fold for the succinyl ester. However, it matters little in the value of  $k_H$  whether an acetyl or succinyl group esterifies ring A of hexachlorophene. Replacement of the phenolic proton on ring B by an acetyl group decreases the rate by  $\sim 300$ -fold for the acetyl ester.

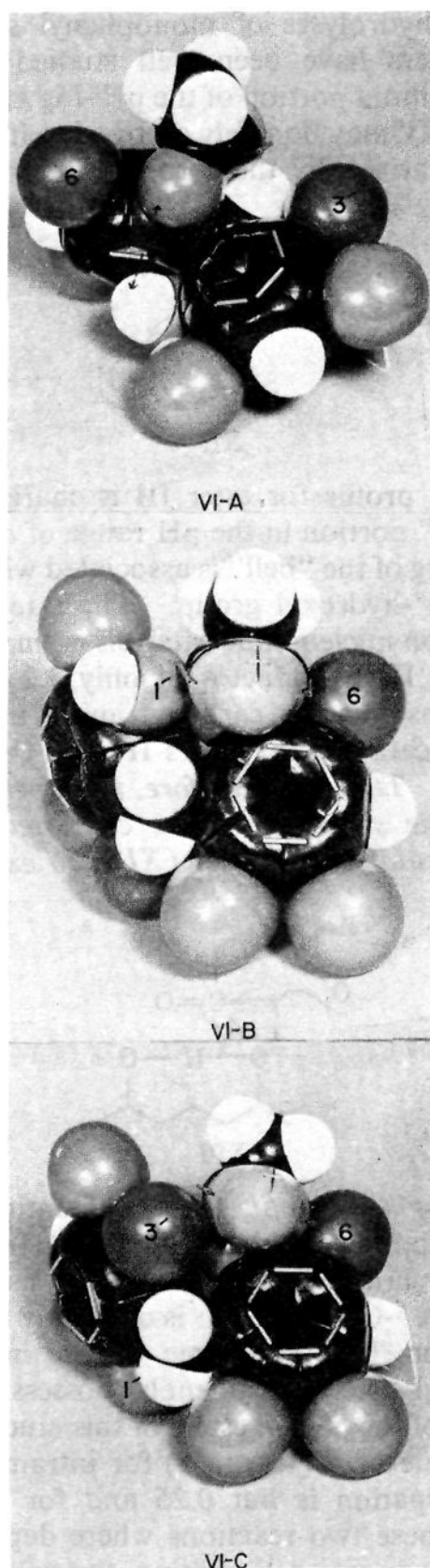
For the alkaline hydrolysis of esters both steric and electronic effects are important.<sup>12-14</sup> The relative rate constants for alkaline hydrolysis of the acetyl esters are provided in Table IV. Examination of Table IV

Table IV. Relative Values of the Second-Order Rate Constants or Lyate Anion Attack on Acetyl Esters

Constant	Rel to $k_{\text{LO}}^{1a}$
$k_{\text{LO}}^{1a}$	1.0
$k_{\text{LO}}^{1b}$	1/28,600
$k_{\text{LO}}^V$	1/92
$k_{\text{LO}}^{11}$	1/142

reveals that acetylation or methylation of the 1'-hydroxyl group decreases the rate as seen for specific acid catalyzed hydrolysis. Most markedly, ionization of the 1'-hydroxyl group results in a  $2.86 \times 10^4$ -fold decrease in the rate constant. Since the rate-determin-

(14) T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, **82**, 3067 (1960).



ing step for reaction of  $\text{LO}^-$  with phenyl acetates is attack of nucleophile and not departure of phenolate leaving group,<sup>9,14</sup> this very large rate deceleration must pertain to the attack step, *i.e.*, electrostatic inhibition of  $\text{LO}^-$  addition to the ester carbonyl carbon upon ionization of the 1'-hydroxyl group or steric hindrance of attack of  $\text{LO}^-$  brought about by a conformational change. The former does not appear likely. If the decrease in rate of  $\text{LO}^-$  attack on I accompanying its ionization is to be attributed to an electrostatic shielding effect by phenoxide ion, then this electrostatic effect would be, by far, the largest yet reported.<sup>15-17</sup> In a rather compre-

(15) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2985 (1969).

(16) T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Donzel, and N. G. Kundu, *J. Amer. Chem. Soc.*, **92**, 1370 (1970).

(17) (a) R. P. Bell and F. J. Lindars, *J. Chem. Soc.*, 4601 (1954); (b) M. L. Bender and Y. L. Chow, *J. Amer. Chem. Soc.*, **81**, 3929 (1959); (c) J. F. Bunnett, *Annu. Rev. Phys. Chem.*, **14**, 271 (1963); (d) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, and G. R. List, *J. Amer. Chem. Soc.*, **86**, 3075 (1964); (e) R. P. Bell and B. A. W. Coller, *Trans. Faraday Soc.*, **61**, 1445 (1965); (f) K. Koehler, R. Skora, and E. H. Cordes, *J. Amer. Chem. Soc.*, **88**, 3577 (1966); (g) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

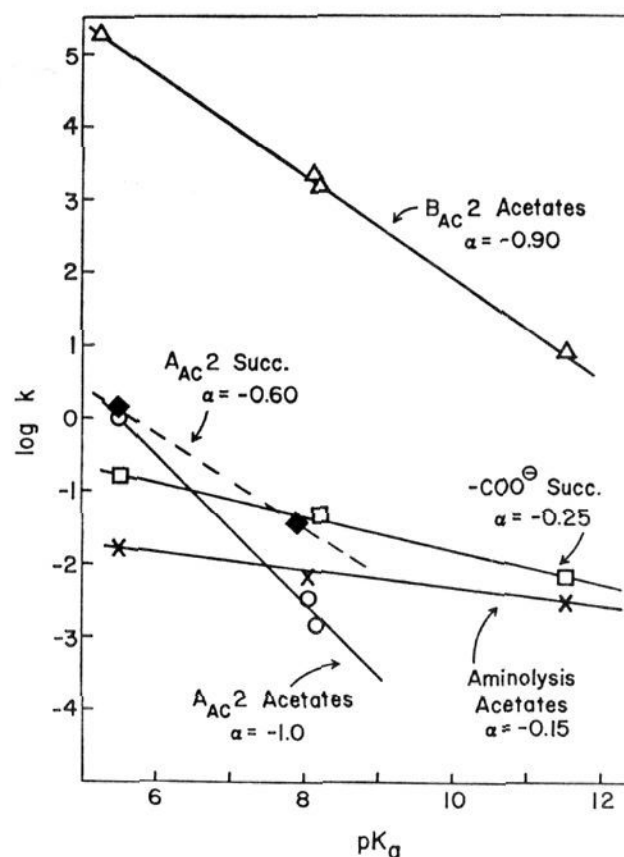
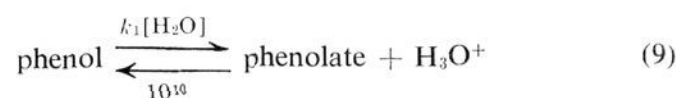


Figure 5. Plots of  $\log k$  vs.  $\text{pK}_a$  values of conjugate acids of the leaving groups.

hensive investigation of the influence of  $\alpha$  substituents on the rate of  $\text{HO}^-$  attack on *o*-nitrophenyl and phenyl acetates, it was concluded that formal ( $-$ ,  $-$ ) ground state charge repulsion to approach of  $\text{HO}^-$  did not occur in aqueous solution.<sup>16,18</sup> It is most likely, therefore, that the *ca.* 30,000-fold decrease in rate of lyate anion attack accompanying ionization of I cannot be attributed to either a polar or an electrostatic effect. It would appear that the same conformational effects required to rationalize the specific acid rate constants must be employed for the specific base rate constants.

Leaving abilities of phenolate ions are related to the  $\text{pK}_a$  values of the corresponding phenols. In Figure 5 are plotted the determined rate constants of this study *vs.* the  $\text{pK}_a$ 's values of the conjugate acids of the leaving groups. Inspection of Figure 5 unequivocally reveals that not only are the logs of the rate constants for  $\text{LO}^-$  attack upon the acetyl esters linear functions of the  $\text{pK}_a$ 's but so too are the logs of the rate constants for aminolysis of the acetyl esters, intramolecular  $-\text{COO}^-$  nucleophilic catalysis of hydrolysis in the succinyl esters, and, most surprisingly, the specific acid catalyzed hydrolysis of both acetyl and succinyl esters (eq 8). The ionization constant of a phenol is provided by the relationships of eq 9 and 10<sup>19</sup>

$$\log k_{\text{nuc}} = \alpha \text{pK}_a + C \quad (8)$$



$$\text{pK}_a = \alpha \log 1/k_1 + C' \quad (10)$$

so that

$$\Delta\Delta F_{\text{nuc}}^\ddagger = -\alpha\Delta\Delta F_{\text{HO}}^\ddagger$$

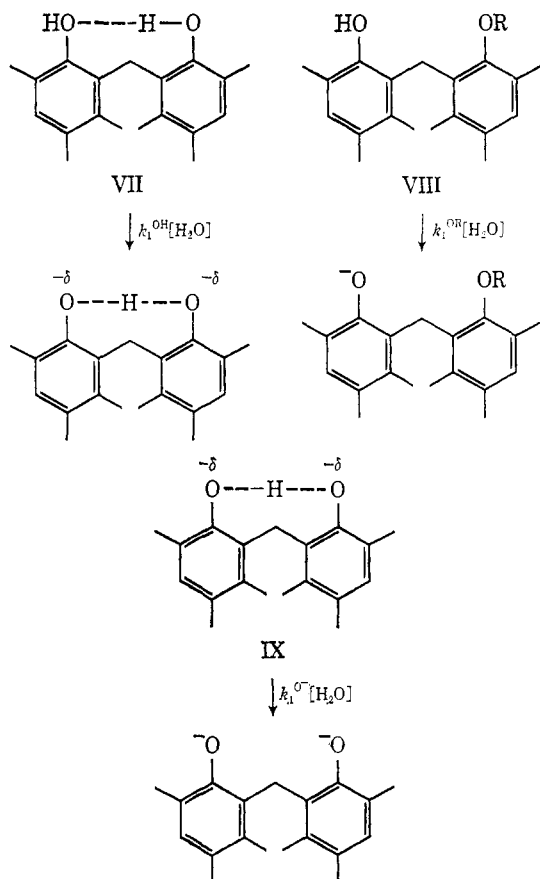
The values of  $\alpha$  (Figure 5) relate the change in free energy of activation for nucleophilic displacement on

(18) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2982 (1969).

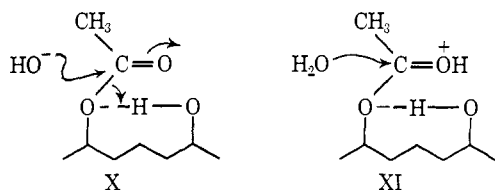
(19) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

ester ( $\Delta\Delta F_{\text{nuc}}^{\ddagger}$ ) to the change in free energy of activation for  $\text{H}_2\text{O}$  attack upon the dissociable proton of the conjugate acid of the leaving group ( $\Delta\Delta F_{\text{HO}}^{\ddagger}$ ). Since  $\alpha = 0.9$  and  $1.0$  for specific acid and specific base catalyzed hydrolysis of the acetyl esters, it follows that the features determining  $k_1$  are of equal importance in determining  $k_{\text{H}}$  and  $k_{\text{LO}}$ . The  $k_1$  values are clearly dictated by the extent of internal hydrogen bonding (Scheme V). From

Scheme V



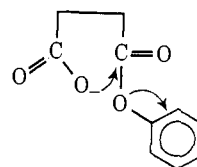
this line of reasoning it would follow that the extent of internal hydrogen bonding determines equally the relative values of  $k_{\text{H}}$  and  $k_{\text{LO}}$ . Here we have a dilemma. The internal hydrogen bonding in X and XI repre-



sents intramolecular general acid catalysis of the breakdown of tetrahedral intermediate to products. However, this step is not rate limiting in  $\text{HO}^-$  catalysis and  $\text{H}_3\text{O}^+$  catalysis is not sensitive to the nature of the leaving group. The dilemma increases when we examine intramolecular carboxyl group catalyzed hydrolysis and aminolysis.

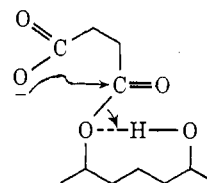
For the hydrolysis of the succinate esters, we may examine the  $\text{pH}-\log k_{\text{obsd}}$  profile (Figure 1) for ester IV. Specific acid catalyzed hydrolysis (Scheme III) heading toward a slope of  $-1$  ( $k_{\text{H}}^{\text{IV}}$ ) is followed by a plateau ( $k_0^{\text{IVa}}$ ) for hydrolysis of the undissociated ester, followed by a sigmoid ascending limb plateauing at higher pH ( $k_0^{\text{IVb}}$ ) associated with hydrolysis of the dissociated

ester. The hydrolyses of monophenyl succinate and glutarate esters have been well studied<sup>20,21</sup> and the ascending sigmoid portion of the  $\text{pH}-\log k_{\text{obsd}}$  profile for both III and IV may be safely ascribed to intramolecular nucleophilic attack by the carboxyl anion (XII). The



XII

$\text{pH}-\log k_{\text{obsd}}$  profile for ester III is characterized by a "bell shaped" portion in the pH range of *ca.* 4–9. The descending leg of the "bell" is associated with the ionization of the 1'-hydroxyl group. The rate constant for carboxyl anion nucleophilic catalysis is smaller for IV as compared to III by a factor of only 3.2 ( $k_0^{\text{IIIb}}/k_0^{\text{IVb}}$ ). The rate constants for carboxyl anion intramolecular nucleophilic catalysis for esters III and IV are actually comparable. There is, therefore, no experimental basis to support the suggestion<sup>2</sup> of a concerted nucleophilic general acid catalyzed reaction (XIII) to explain the bell



XIII

shaped  $\text{pH}-\log k_{\text{obsd}}$  profile for III. Continuing further, it is known that the rate-determining step for intramolecular nucleophilic catalyzed hydrolysis of phenyl acylate by the  $-\text{COO}^-$  group is departure of the leaving phenoxide ion.<sup>20,22</sup> The same is true in the aminolysis of acetyl esters of phenols possessing basicities in the range of the phenyl esters of this study.<sup>9,23</sup> However, the value of  $\alpha$  (Figure 5) for intramolecular carboxyl participation is but 0.25 and for aminolysis is 0.15. For these two reactions where departure of the leaving group is rate determining, the value of  $\alpha$  is less than for specific base catalysis ( $\alpha = 0.9$ ) where attack is rate limiting. If it is assumed that the 1'-hydroxyl group is acting as a general acid catalyst for leaving group departure, then it would follow that this catalysis is assisting most in that step which is kinetically unimportant. The  $\alpha$  value for specific acid catalyzed hydrolysis of the acetyl esters equals 1.0. Though Kirby<sup>11</sup> makes a cogent argument for leaving group departure as being partially rate limiting and subject to general acid catalysis in the  $\text{H}_3\text{O}^+$  catalyzed hydrolysis of esters, the insensitivity of the  $A_{\text{Ac}^2}$  mechanism to leaving group tendency makes it highly unlikely that its  $\alpha$  value of 1.0 could be due to intramolecular general acid catalysis. A change in rate-limiting step from departure to attack for intramolecular  $-\text{COO}^-$  catalyzed

(20) (a) E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, **82**, 5328 (1960); (b) T. C. Bruice and U. K. Pandit, *ibid.*, **82**, 5858 (1960); (c) T. C. Bruice and W. C. Bradbury, *ibid.*, **87**, 4846, 4851 (1965); (d) *ibid.*, **90**, 3808 (1968).

(21) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970).

(22) R. Goiten and T. C. Bruice, *J. Phys. Chem.*, **76**, 432 (1972).

(23) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 4729 (1972).

hydrolysis and aminolysis is required in order to explain the small  $\alpha$  for these two cases. This would require a considerable increase in rate due to intramolecular phenolic group participation. We have already seen that the 1'-hydroxyl group provides only a threefold rate enhancement for intramolecular  $\text{-COO}^-$  nucleophilic catalysis in III. Much the same is true for the aminolysis reaction. Examination of Table IV reveals that the ratios of  $k_n^I/k_n^{II}$  range from *ca.* 1.5 to 2.5, the ratios  $k_n^{I^-}/k_n^{II}$  range from 0.5 to 1.5, while the ratios for  $k_n^I/k_n^{I^-}$  range from 1.1 to 3.8. Thus, in the aminolysis reaction changes in rate brought about by methylation of the 1'-HO group or its ionization appear quite minimal (small  $\alpha$  value). Continuing further, though intramolecular hydrogen bonding determines  $k_1^{O^-}$  for the ionization of VII, there is no analogy in the hydrolytic reactions where there is no possibility of hydrogen bonding.

We have shown that factors determining  $k_1^{OH}$ ,  $k_1^{OR}$ , and  $k_1^{O^-}$  (Scheme V) are important in determining the relative values of the  $k_H$  and  $k_{LO}$  constants for acetyl ester hydrolysis, the  $k_n$  values for aminolysis of acetyl esters, and the rate constants for  $\text{-COO}^-$  participation in succinate ester hydrolysis. However, it has also been shown that the intramolecular hydrogen bonding (or its absence) which determines the  $k_1$  values cannot logically be employed to rationalize the various rate constants for the esters of this study. It is useful at this point to paraphrase a story once told by a famous physical organic chemist to his students. Long ago an advertising firm noted that in a local area there was a direct relationship between an increase in the purchase of newspapers and brassieres by women. They concluded that an increase in literacy led to the wearing of brassieres. In truth, the increase in sales of newspapers and brassieres was due to a reopening of the weaving mills and an associated increase in the women's purchasing power. It is suggested that the "weaving mills" of this study are the conformations possessed in common by VII, VIII, and IX and the ester species possessing like sub-

stituents at the 1' position of the B ring. It is required, on the basis of what has been discussed, that the steric demands of the various substituents on the 1 position control the rates of nucleophilic attack rather than the rates of departure of the leaving group. This requirement is necessary in order to provide for the large values of  $\alpha$  for those reactions in which nucleophilic attack is rate controlling and the small values of  $\alpha$  (brought about by small changes in the standard free energy for tetrahedral adduct formation) for those reactions in which departure of the leaving group is rate controlling. Reasonable suggestions for the conformations controlling both the  $pK_a$  of the conjugate acids of the leaving groups and ester hydrolysis follow. The conformation of the ester with a hydroxyl group at the 1' position is likely weighted most heavily in favor of rotamer VIA. A like rotamer distribution is suggested for VII in which a slight rotation (dashed line between the hydrogen at 1' and ester oxygen) allows internal hydrogen bonding. In VIA steric hindrance by the 3'- and 6-chloro substituents to approach of a nucleophile at a right angle to the ester carbonyl group is minimal. Alkylation of the 1'-hydroxyl function results in an increase in steric demand at the 1' position and an increase in the population of rotamer VIC. In VIC the 3'- and 6-chloro substituents hinder approach of the nucleophile to the ester carbonyl group. Ionization of the 1'-hydroxyl group may also result in an increase in the population of rotamer VIC and in addition VIB. The formation of VIB and VIC on ionization of the 1'-hydroxy group is attributed to charge repulsion between the 1' substituent and the  $\pi$ -electron cloud of the A ring and to greater steric demand of the phenoxy anion as compared to the phenol. For conformation VIB internal hydrogen bonding of the 1'-hydroxyl to the 1-oxyanion is favored as in IX, and maximal steric hindrance to nucleophilic attack is present.

**Acknowledgment.** This work was supported by a grant from the National Institutes of Health.