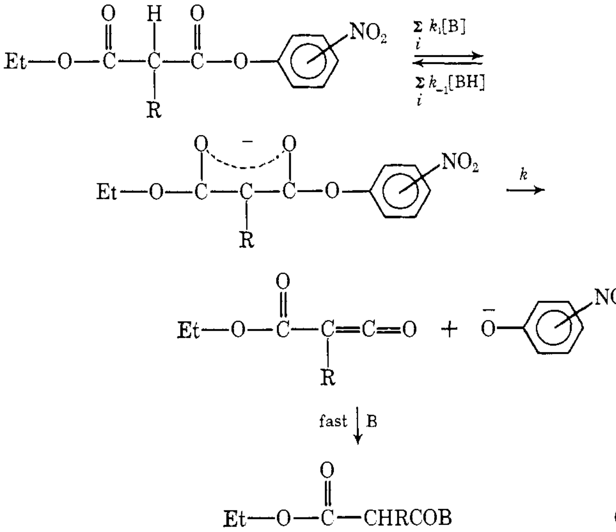
The Carbanion Mechanism (E1cB) of Ester Hydrolysis. III. Some Structure–Reactivity Studies and the Ketene Intermediate

R. F. Pratt[1a] **and Thomas C. Bruice**[1b]

Contribution from the Department of Chemistry,
University of California at Santa Barbara, Santa Barbara, California 93106.
Received March 24, 1970

Abstract: The hydrolyses of carboxylic acid esters I–XVII have been studied kinetically in order to further establish the E1cB mechanism as an acyl transfer path for esters. The principal feature of this mechanism is elimination of the leaving group from the carbanion formed from the ester by ionization at a position α to the ester group. Such carbanion species were observed spectrophotometrically with all of the above esters and appeared during hydrolysis under conditions ranging from steady state through fast preequilibrium. The nature of the leaving group has emerged as an extremely important factor in determining the relative contributions of the E1cB and BAc2 mechanisms. Yields of acetoacetanilide obtained from hydrolysis of *p*-nitrophenyl acetoacetate in the presence of aniline buffers have been examined in detail and compared with the kinetics of *p*-nitrophenol release. These results as well as those establishing a change of rate-limiting step with increase in general base concentration and the deuterium solvent isotope effect are fully in accord with an E1cB hydrolysis mechanism which proceeds by way of a transient free ketene after elimination of the leaving group from the carbanion.

Studies in this laboratory[2a,b] have revealed the existence of a new mechanism of nucleophilic substitution reactions of esters. The kinetics of these reactions of *o*- and *p*-nitrophenyl acetate esters with electron withdrawing and delocalizing α substituents are consistent with an E1cB mechanism. This mechanism involves a reactive carbanion species which decomposes to products probably by way of a short-lived ketene intermediate, *e.g.*, eq 1.



(1)

Recent publications have emphasized the more usual inertness of carbanions of both carboxylate[3] and sulfonate[4] esters (although, with regard to the latter, the results of Hoogenboom, *et al.*,[5] should be noted).

The following work was undertaken to further demonstrate the characteristics of the E1cB mechanism in reactions of this type and to define more closely the circumstances under which it can be observed.

Experimental Section

Materials. Reagent grade potassium chloride, anhydrous potassium carbonate, and sodium borate were used without further purification. Hydrazine monohydrochloride was twice recrystallized from aqueous ethanol. Reagent grade aniline was distilled at atmospheric pressure (bp 185°) from zinc dust and stored in the dark under nitrogen. Aqueous solutions were prepared from deionized freshly double glass distilled water. Dioxane and acetonitrile were of spectroquality (Matheson Coleman and Bell).

Yields are not reported for the following preparations since no effort was made to maximize them. Yields of the diketene reactions were essentially quantitative. Analyses were performed by Alfred Bernhardt, Max Planck Institute, West Germany.

Ethyl *p*-nitrophenyl malonate (I) and ethyl *o*-nitrophenyl malonate (II) were prepared by the methods of Holmquist and Bruice.[2a] The former compound was purified by column chromatography (eluted with 1:1 benzene–chloroform from a silica gel column) and had mp 61–62° after recrystallization from benzene–petroleum ether (lit.[2a] mp 60–60.5°). The ortho ester was purified by zone sublimation as described previously.[2a]

***p*-Nitrophenyl Ethyl Thiol Malonate (III).** To a solution of 2.42 g (0.02 mol) of malonyl dichloride in 40 ml of dry benzene, stirred at room temperature, was added a mixture of equivalent amounts (0.02 mol each) of triethylamine and ethane thiol dissolved in 10 ml of dry benzene. The mixture was stirred for 0.5 hr (triethylamine hydrochloride precipitated), 3.24 g (0.02 mol) of sodium *p*-nitrophenoxide was added to it, and the stirring continued for a further hour. Removal of the insoluble material by filtration followed by evaporation of the benzene yielded an orange-brown oil which was purified by chromatography as for ester I. The first colored fraction from the column yielded a pale yellow oil which crystallized on standing. Three recrystallizations of this material from benzene–petroleum ether gave a white crystalline solid, mp 71–72°. The infrared spectrum (KBr) showed strong absorptions at 1670 and 1765 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.05; H, 4.12; N, 5.20. Found: C, 48.79; H, 4.37; N, 5.35.

Ethyl 2,2,2-Trifluoroethyl Thiol Malonate (IV). 2,2,2-Trifluoroethane thiol was prepared by the method of Gregory and Bruice,[6] bp 35–36° (1 atm) (lit.[6] bp 37–40°), n^{25}D 1.3450. Ester IV was prepared from this thiol and ethyl malonyl chloride in the presence of triethylamine in a manner similar to that employed for III.

---

[1] (a) Postdoctoral Fellow, Department of Chemistry, University of California at Santa Barbara; (b) to whom inquiries should be addressed.

[2] (a) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2993 (1969); (b) B. Holmquist and T. C. Bruice, *ibid.*, **91**, 3003 (1969).

[3] (a) P. S. Tobias and F. J. Kézdy, *ibid.*, **91**, 5171 (1969); (b) T. C. Bruice, A. F. Hegarty, S. M. Felton, A. Donzel, and N. G. Kundu, *ibid.*, **92**, 1370 (1970).

[4] P. Müller, D. F. Mayers, D. R. Zaborsky, and E. T. Kaiser, *ibid.*, **91**, 6732 (1969).

[5] B. E. Hoogenboom, M. S. El-Faghi, S. C. Fink, E. D. Hoganson, S. E. Lindberg, C. L. Linn, D. J. Nelson, J. O. Olson, L. Rennerfeldt, and K. A. Wellington, *J. Org. Chem.*, **34**, 3414 (1969).

[6] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2121 (1967).

The product was distilled through a spinning band column, bp 88° (3.5 mm), n^{25}D 1.4212. Strong absorptions were observed at 1705 and 1740 cm^{-1} in the infrared spectrum.

Anal. Calcd for $C_7H_9F_3O_3S$: C, 36.44; H, 3.91; S, 13.93; F, 25.20. Found: C, 36.85; H, 3.66; S, 14.06; F, 25.10.

Phenyl acetoacetate (V) and *p*-**chlorophenyl acetoacetate** (VI) were prepared by the method of Lacey.[7] The former had mp 47–48° (lit.[7] mp 48–49°) after two recrystallizations from benzene–petroleum ether and the latter had mp 52–53° (lit.[7] mp 54–56°) after three recrystallizations from the same solvent.

This preparative method (refluxing a benzene solution of the phenol and diketene in the presence of a catalytic amount of triethylamine) failed with the more acidic phenols where the reaction yielded only the unchanged phenol and dehydroacetic acid. The following aryl esters were obtained by stirring together (room temperature, overnight) equivalent amounts of the phenol and diketene with a drop of triethylamine in dichloromethane solution. The products were recrystallized several times from dichloromethane–petroleum ether (with the temperature of solutions not greater than 40°).

m-**Chlorophenyl acetoacetate** (VII) showed mp 40–41°. *Anal.* Calcd for $C_{10}H_9ClO_3$: C, 56.48; H, 4.27; Cl, 16.68. Found: C, 56.57; H, 4.33; Cl, 16.67.

p-**Carbomethoxyphenyl acetoacetate** (VIII) showed mp 110–111°. *Anal.* Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.72; H, 5.18.

p-**Acetylphenyl acetoacetate** (IX) exhibited mp 104–105°. *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.84; H, 5.34.

m-**Nitrophenyl acetoacetate** (X) showed mp 73–74°. *Anal.* Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 54.00; H, 4.08; N, 6.34.

p-**Nitrophenyl acetoacetate** (XI) showed mp 71–72°. *Anal.* Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.73; H, 4.11; N, 6.33.

The following alkyl acetoacetates were prepared in the same way as the latter aryl acetoacetates.

Trifluoroethyl acetoacetate (XII) showed bp 74–75° (20 mm), n^{25}D 1.3728. *Anal.* Calcd for $C_6H_7F_3O_3$: C, 39.14; H, 3.83; F, 30.94. Found: C, 39.17; H, 3.80; F, 31.15.

Propargyl acetoacetate (XIII) showed bp 106–108° (20 mm), n^{25}D 1.4505 (lit.[8] bp 97–100° (11 mm), n^{20}D 1.4551). *Anal.* Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 60.27; H, 6.01.

2-Methoxyethyl acetoacetate (**XIV**) showed bp 118–120° (20 mm), n^{25}D 1.4360. *Anal.* Calcd for $C_7H_{12}O_4$: C, 52.48; H, 7.55. Found: C, 52.56; H, 7.58.

Benzophenone oxime acetoacetate (**XV**) was obtained as a colorless oil which could not be crystallized, nor could it be distilled or zone sublimed because of decomposition at the temperatures required. It was purified by chromatography as for I. *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38; N, 4.98. Found: C, 72.44; H, 5.43; N, 4.63.

p-**Nitrobenzaldehyde oxime acetoacetate** (**XVI**) showed mp 121–122° (from dichloromethane–petroleum ether). *Anal.* Calcd for $C_{11}H_9N_2O_5$: C, 53.01; H, 3.64; N, 11.24. Found: C, 53.17; H, 4.20; N, 11.69.

Commercial **ethyl acetoacetate** (XVII) was distilled and a fraction of bp 73–75° (18 mm), n^{25}D 1.4172 used.

Acetoacetanilide was prepared by the method of Williams and Krynitsky.[9] Recrystallization from diisopropyl ether yielded material of mp 81–82° (lit.[9] mp 84–85°).

Phenyl cyanoacetate, mp 43°, was available from a previous study in this laboratory.[3]

Kinetic Measurements. All reactions studied kinetically were carried out in water at μ = 1.0 (with KCl), at a temperature of 30 ± 0.1°, and followed spectrophotometrically. Reactions whose half-lives fell between 10 sec and 5 hr were carried out in a Radiometer pH-stat assembly specifically designed for a Cary 15 spectrophotometer;[10] the use of this apparatus removed complications due to the presence of buffer species and made the determination of background hydrolytic rates much easier (see Results). A Gilford Model 2000 spectrophotometer and a Durrum-Gibson Model 13001 stopped flow spectrophotometer were used to follow slower and faster reactions, respectively; buffered solutions were required here of course.

With the exception of special cases, discussed later, all hydrolyses were studied under conditions such that the disappearance of the ester and the appearance of the product phenol or alcohol occurred at the same rate and in a manner described by pseudo-first-order kinetics. At high pH there was evidence of rapid carbanion formation with all the esters investigated. This is not surprising since both malonate and acetoacetate esters are well known to have appreciably acidic hydrogens at the α-carbon position.[11]

The carbanion species were observed in the uv spectra as absorptions at higher wavelength and greater intensity than those of the original esters. Their presence could be demonstrated even in the cases of the extremely reactive nitrophenyl esters. For instance, optical densities at a given wavelength of solutions of ester III in 0.025 *M* potassium hydroxide were obtained by the extrapolation to zero time of measurements of optical density *vs.* time obtained under stop-flow conditions. The extrapolation procedure was of course needed because of the very rapid hydrolysis of this ester. When the optical densities at a series of wavelengths had been examined in this way a spectrum of the ester in alkaline solution was available. An absorption maximum was obtained at 295 nm ($\log \epsilon \sim 4.67$) *cf.* the neutral ester λ_{max} 268.5 nm ($\log \epsilon \sim 4.13$).

For the hydrolyses of esters I–III and XI, it was necessary to obtain background lyate hydrolysis rates between pH 8 and 10 from extrapolation to zero buffer concentration of stop-flow rates done in buffered solution. The accuracy of intercepts for such extrapolations is not great because of a combination of the following: (a) fast stop-flow rates were, on the average, not reproducible to less than 5%; (b) plots of observed rate constants *vs.* buffer concentration were nonlinear, the curvature increasing at low buffer concentration; (c) difficulties of keeping the final pH constant at low buffer concentration. It was necessary with these very reactive esters to mix in the stop-flow apparatus a solution of the buffer with a solution of the ester in KCl solution at pH 3. At low buffer concentration, therefore, a considerable change in pH occurred and so considerable trial and error was needed in adjusting the pH of buffers of different buffer concentration to yield the same pH on mixing. Clearly then, at low buffer concentration, where greatest accuracy was desirable, the least accuracy was experimentally possible. The uncertainties thus present were not large enough to cause any serious doubt as to the overall shape of the pH–rate profile, particularly since they only apply to points in the pH range 8–10 where the profile curves are linear. The buffers used were hydrazine, borate, and carbonate. For pH > 11 potassium hydroxide solutions could be used.

Reactions under other than stop-flow conditions were initiated by addition of the ester in dioxane or acetonitrile solution to the buffered or pH-statted aqueous solution to give final concentrations of ester and organic solvent of 10^{-5}–10^{-4} *M* and 1%, respectively. Usually dioxane was used as the organic solvent but its replacement by acetonitrile did not significantly affect measured rates. An exception here was the thiol ester (IV). In this case, using dioxane, the reaction could not be followed satisfactorily at wavelengths where the product thiol or thiolate anion absorbed, presumably because of reaction of these species with trace amounts of peroxide in the dioxane. Better results were obtained here when acetonitrile was used.

The wavelengths used to follow the hydrolysis rates spectrophotometrically are shown in Table I. Reaction rates were followed for at least three half-lives and pseudo-first-order rate constants

Table I. Wavelengths Used in the Spectrophotometric Determination of Hydrolysis Rates

Esters	Wavelength, nm	
I, III, XI	347	*p*-Nitrophenol or *p*-nitrophenoxide release
	268	Ester disappearance
II	372	*o*-Nitrophenol or *o*-nitrophenoxide release
IV	280	Carbanion disappearance (pH >7)
	240	Ester disappearance
V–VII, XII–XVII	270–280	Carbanion disappearance (pH >7)
VIII	300	*p*-Carbomethoxy phenoxide release
IX	320	*p*-Acetyl phenoxide release
X	400	*m*-Nitrophenoxide release

---

(7) R. N. Lacey, *J. Chem. Soc.*, 854 (1954).

(8) R. N. Lacey, *ibid.*, 827 (1954).

(9) J. W. Williams and J. A. Krynitsky, *Org. Syn.*, **21**, 4 (1941).

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

(11) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 161.

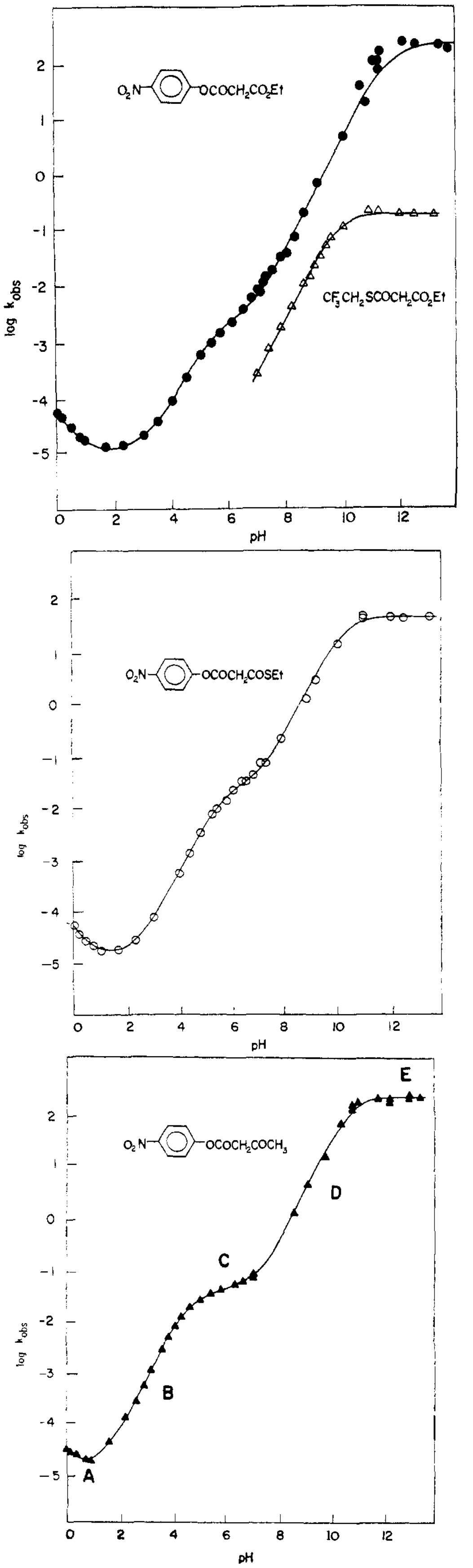


Figure 1. Plots of log k_{obsd} (k_{obsd} in sec^{-1}) *vs.* pH for the hydrolyses of esters I (●), III (○), XI (▲), and IV (△).

were calculated in the usual way from measured infinity values or by the method of Guggenheim.[12]

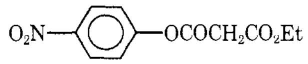
D_2O Solvent Isotope Effects. These experiments were carried out in D_2O to which appropriate quantities of solid potassium hydroxide were added.

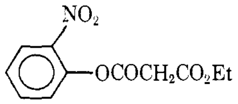
Product Analysis. In the case of the hydrolysis of *p*-nitrophenyl acetoacetate in aniline buffers, analyses were carried out for acetoacetanilide. Thin-layer chromatography (silica gel–chloroform or benzene) of samples of typical kinetic reaction mixtures showed an iodine staining spot of the same color and R_f as acetoacetanilide. Quantitative analyses were carried out as follows.

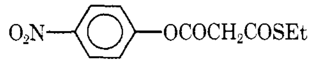
A pellet of solid potassium hydroxide was added to 25-ml reaction mixtures containing 1.2×10^{-4} *M* ester in aniline buffers [30°, μ = 1 (KCl), 1% dioxane] after release of *p*-nitrophenol was complete. This raised the pH to $\geq$12.5 (the pK_a of the anilide, by spectrophotometric titration, was 10.5). The solutions were then extracted with three 10-ml portions of dichloromethane. Spectra of the aqueous solutions after extraction showed absorption maxima at 405 (*p*-nitrophenoxide) and 296 nm (acetoacetanilide anion). Routinely, for analysis, optical densities at 296 nm were recorded. Prepared at the same time in the same aniline buffers were samples containing (a) 1.2×10^{-4} *M* *p*-nitrophenol and (b) 1.2×10^{-4} *M* each of *p*-nitrophenol and acetoacetanilide, and optical densities of these solutions at 296 nm were also recorded after extraction. From these results the fraction of *p*-nitrophenyl acetoacetate converted to acetoacetanilide could be obtained. This analysis was performed under varying conditions of pH and aniline concentration. It was noted that under the above conditions the other product of *p*-nitrophenyl acetoacetate hydrolysis (acetoacetate) did not absorb at 296 nm and that no acetoacetanilide hydrolysis occurred in the time required for analysis.

Results

The hydrolyses of esters I–XVII have been investigated.

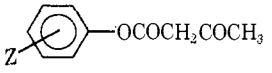

I


II


III

$CF_3CH_2SCOCH_2CO_2Et$

IV



V, Z = H
VI, Z = *p*-Cl
VII, Z = *m*-Cl
VIII, Z = *p*-CO_2Me
IX, Z = *p*-COMe
X, Z = *m*-NO_2
XI, Z = *p*-NO_2

$ROCOCH_2COCH_3$

XII, R = CF_3CH_2–
XIII, R = $CH{\equiv}C{-}CH_2$–
XIV, R = $CH_3OCH_2CH_2$–
XV, R = $Ph_2C{=}N$–
XVI, R = *p*-$NO_2{-}C_6H_4C{=}N$–
XVII, R = CH_3CH_2–

Nitrophenol Esters. A plot of log k_{obsd} *vs.* pH for the observed first-order hydrolytic rates for the *p*-nitrophenol esters I, III, and XI is shown in Figure 1. The points on this plot are experimental and the lines are theoretical, having been derived from the empirical eq 2. Unexpectedly large differences were observed

$$k_{obsd} = k_{H_2O} + k_H a_H + k_a \frac{K_{a_1}}{K_{a_1} + a_H} + k_b \frac{K_{a_2}}{K_{a_2} + a_H} \qquad (2)$$

between the curve obtained here for ethyl *p*-nitrophenyl malonate and that reported previously by Holmquist and Bruice[2a] for ethyl *o*-nitrophenyl malonate. Hydrolysis of the *o*-nitrophenyl ester II was repeated be-

---

(12) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

Table II. Empirical Constants Used to Define pH-Rate Profiles of Esters I-III and XI

Ester	$k_{H_2O} \times 10^5$, sec^{-1}	$k_H \times 10^5$, sec^{-1} M^{-1}	k_a, sec^{-1}	k_b, sec^{-1}	K_{a_1}, M	K_{a_2}, M
I	1.3	4.2	2.5×10^{-3}	220	3.3×10^{-6}	2.3×10^{-12}
II	1.2[a]		3.5×10^{-3}	100[a]	1.1×10^{-5}	1.2×10^{-12}
III	1.6	3.7	3.3×10^{-2}	57	1.94×10^{-6}	4.0×10^{-11}
XI	1.3	1.9	4.0×10^{-2}	185	1.4×10^{-5}	1.06×10^{-11}

[a] The original values of Holmquist and Bruice.[2a]

Table III. Plateau Rates and Deuterium Isotope Effects for the Hydrolyses of the Acetoacetate Esters[a]

	k_p, sec^{-1}				
Ester	0.05 M KOH	0.25 M KOH	0.05 M KOD	0.25 M KOD	k_{H_2O}/k_{D_2O}[b]
III	61		47		1.3
IV	0.19	0.19	0.135	0.137	1.4
V	0.056	0.053	0.038	0.035	1.45
VI	0.25	0.24	0.19		1.35
VII	0.90	0.90	0.71	0.67	1.3
VIII	8.2	7.9			
IX	18.4	18.4			
X	6.59	6.00	5.36	5.00	1.2
XI	193		166	170	1.15
XII	9.13×10^{-4}	8.89×10^{-4}			
XIII	7.55×10^{-4}	7.55×10^{-4}			
XIV	7.14×10^{-4}	6.92×10^{-4}			
XV	1.44×10^{-3}	1.41×10^{-3}			
XVI	4.33×10^{-3}	4.80×10^{-3}			
XVII	6.27×10^{-4}	6.21×10^{-4}	4.50×10^{-4}	4.44×10^{-4}	1.4
Phenyl cyanoacetate	0.058	0.056	0.042	0.040	1.4

[a] Solvent, H_2O; 30°; μ = 1.0 with KCl. [b] Obtained by averaging values for H_2O and D_2O solutions and rounding off their quotient to 0.05.

tween pH 3 and 8 and the results are shown in Figure 2. The reason for the discrepancy with the earlier results lies with the method of obtaining lyate hydrolysis rates. In the earlier study the pseudo-first-order rate constants for lyate species catalysis were obtained by extrapolation of plots of k_{obsd} *vs.* [buffer] to [buffer] = 0. For buffer acids of $pK_a > 8$ a downward curvature of the plots of k_{obsd} *vs.* [buffer] were noted signifying a change in rate-limiting step. This curvature was taken into account in extrapolation of k_{obsd} to [buffer] = 0. In the case of buffer acids of $pK_a < 8$, however, linear plots were obtained. In the present study buffers were not employed since k_{obsd} values for solvolysis were obtained *via* a spectrophotometric pH-stat. Values of k_{obsd} for lyate species catalysis obtained in this manner are smaller than those obtained in the previous study. The disparity arises from the fact that all k_{obsd} *vs.* [buffer] plots are curved but the curvature for buffer acids of $pK_a < 8$ is not noticeable until a concentration of buffer is obtained which is below the buffering capacity of the solution—at a buffer concentration below that employed in the previous study. Best values for the empirical constants of eq 2 for the nitrophenol esters (I, II, III, XI) are given in Table II. Rate constants determined for the hydrolysis of the thiol malonate IV are also shown in Figure 1.

Aryl and Alkyl Acetoacetates. At high pH the rates of hydrolysis of esters V–XVII approached a constant value, a plateau rate (k_p). Values of k_p were obtained for these esters by following hydrolysis rates in potassium hydroxide solutions (Table III). Also included in Table III are rate constants obtained under the same conditions in D_2O solutions and the derived k_{H_2O}/k_{D_2O} values. These constants are also provided for the malonates III and IV and phenyl cyanoacetate.

A plot of log k_p *vs.* σ^-[13] for the aryl acetoacetates V–XI (not shown) has a slope (ρ^-), determined by a least-squares treatment, of 2.8. The correlation with σ^- is far better than that with σ. In Figure 3 a plot of log k_p *vs.* pK_a of the leaving group[14] is presented for

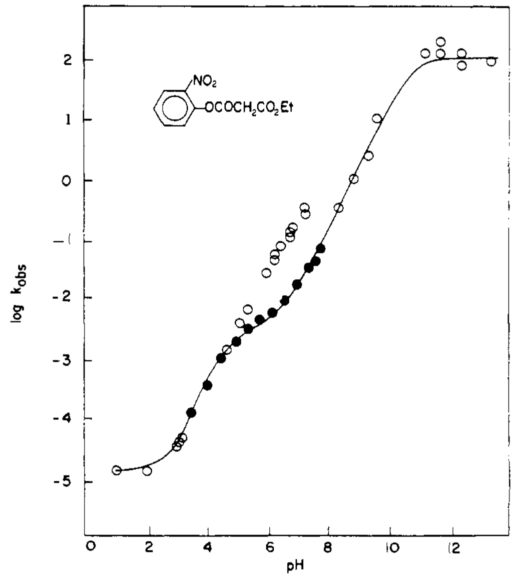


Figure 2. Plot of log k_{obsd} (k_{obsd} in sec^{-1}) *vs.* pH for the hydrolysis of ethyl *o*-nitrophenyl malonate (II): Holmquist and Bruice[2a] (○) and present work (●).

---

[13] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, Chapter 7.

[14] pK_a values used here are from the tables in Chapter 8 of A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. Spectrophotometric pK_a values obtained as part of this work for benzophenone oxime and *p*-nitrobenzaldehyde oxime were 11.3 and 9.8, respectively.

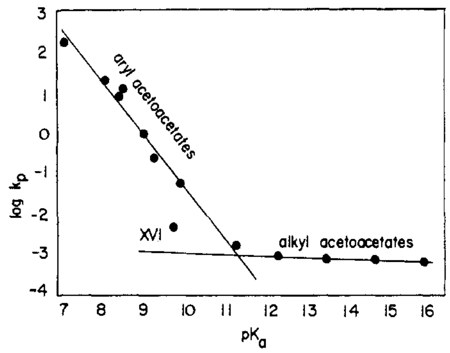


Figure 3. A plot of log k_p (k_p in units of $\sec^{-1}$) *vs.* pK_a of the conjugate acid of the leaving group for the acetoacetate esters V–XVII.

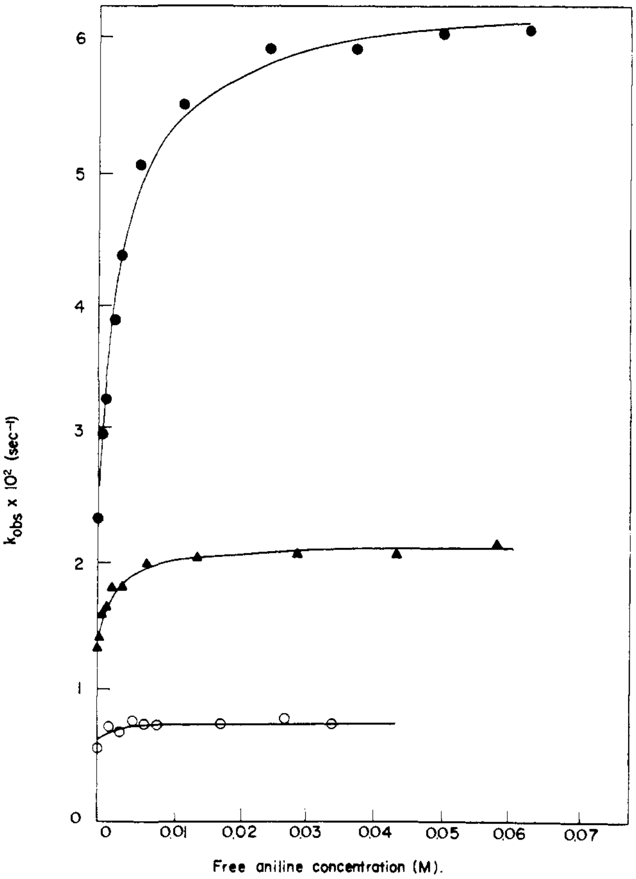


Figure 4. Plots of k_{obsd} *vs.* free aniline concentration for the hydrolysis of *p*-nitrophenyl acetoacetate (XI) in aniline buffers at pH 5.1 (●), 4.6 (▲), and 4.1 (○).

the acetoacetates. The slope of the best straight line through the aryl acetoacetates is −1.29 and that through the alkyl acetoacetates (excluding the oxime esters XV and XVI) is −0.05.

Hydrolysis of *p*-Nitrophenyl Acetoacetate in Aniline Buffers. A plot of pseudo-first-order rate constants *vs.* free aniline concentration[15] for the hydrolysis of ester XI in aniline buffers at various pH's is shown in Figure 4. The fraction (f) of the ester converted to acetoacetanilide during hydrolyses under the same conditions is presented as Figure 5.

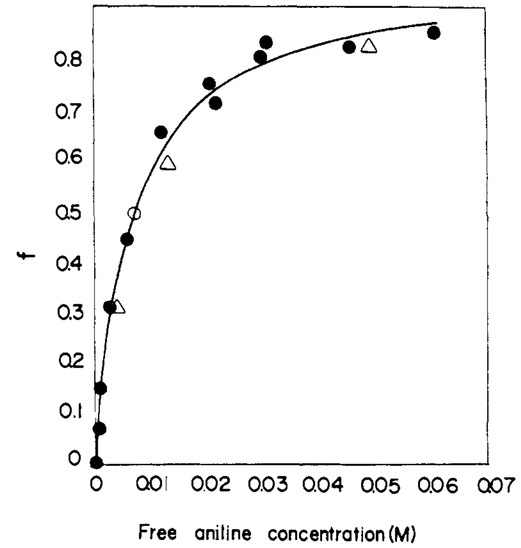


Figure 5. A plot of the fraction (f) of *p*-nitrophenyl acetoacetate converted to acetoacetanilide on hydrolysis in aniline buffers at pH 5.1 (●), 4.6 (▲), and 4.1 (○).

Discussion

Holmquist and Bruice[2a] have proposed an E1cB mechanism for the hydrolysis (and acyl transfer reactions in general) of certain malonate esters. The features of this mechanism are carbanion formation by removal of a proton from a carbon atom α to the ester group and elimination of the leaving group from the carbanion, directly, or in a solvent-mediated manner (see below), to yield the products, *i.e.* eq 3, where $k_0 = k_{H_2O} + k_H[H^+]$

$$\begin{tikzcd}
\mathrm{SH} \arrow[r, shift left, "{k_1[\mathrm{H_2O}],\ k_2[\mathrm{OH^-}]}"] \arrow[rr, bend left, "k_0"] & \mathrm{S}^- \arrow[l, shift left, "{k_{-1}[\mathrm{H^+}],\ k_{-2}[\mathrm{H_2O}]}"] \arrow[r, "k_3"] & \text{products}
\end{tikzcd} \qquad (3)$$

representing normal Ac2 mechanisms at low pH.

Making a steady-state assumption with respect to the concentration of S^- the following equation for observed pseudo-first-order rate constants can be derived (eq 4).

$$k_{obsd} = k_0 + \left(\frac{k_1k_3}{(k_{-2} + k_3)}\right)\left\{\frac{(k_{-2} + k_3)/k_{-1}}{[(k_{-2} + k_3)/k_{-1}] + a_H}\right\} + \frac{k_2k_3[OH^-]}{k_{-2} + k_3}\left\{\frac{(k_{-2} + k_3)/k_{-1}}{[(k_{-2} + k_3)/k_{-1}] + a_H}\right\} \qquad (4)$$

This equation should be compared with the empirical eq 2 describing the experimental results.

At low pH ($a_H \gg K_{a_2}$) eq 2 becomes eq 5 and this is of

$$k_{obsd} = k_0 + k_a\frac{K_{a_1}}{K_{a_1} + a_H} + k_b\frac{K_{a_2}}{K_w}[OH^-] \qquad (5)$$

the same form as eq 4 if the third term becomes important $(k_{-2} + k_3)/k_{-1} > a_H$ so that eq 4 can be written as

$$k_{obsd} = k_0 + \frac{k_1k_3}{k_{-2} + k_3}\,\frac{(k_{-2} + k_3)/k_{-1}}{[(k_{-2} + k_3)/k_{-1}] + a_H} + \frac{k_2k_3[OH^-]}{k_{-2} + k_3}$$

Hence

$$k_a = (k_1k_3)/(k_{-2} + k_3) \qquad (6)$$

$$K_{a_1} = (k_{-2} + k_3)/k_{-1} \qquad (7)$$

---

[15] The pK_a of aniline [30°, μ = 1 (KCl), 1% dioxane] was determined spectrophotometrically to be 4.80.

Table IV. Rate Constants for the Hydrolyses of the Nitrophenol Esters I–III and XI[a]

Ester	k_1, sec^{-1}	k_{-1}, sec^{-1} M^{-1}	k_2, sec^{-1} M^{-1}	k_{-2}, sec^{-1}	k_3, sec^{-1}	pK_a
I	2.66×10^{-3}	7.1×10^{7}	3.62×10^{4}	14.3	220	10.4
II	3.60×10^{-3}	0.93×10^{7}	8.20×10^{4}	3.1	100	9.4
III	3.44×10^{-2}	3.06×10^{7}	1.88×10^{4}	2.5	57	9.0
XI	4.0×10^{-2}	1.33×10^{7}	1.32×10^{5}	0.65	185	8.5

[a] Solvent, H_2O; 30°; $\mu = 1.0$ with KCl.

and

$$k_b \frac{K_{a_2}}{K_w} = \frac{k_2 k_3}{k_{-2} + k_3} \tag{8}$$

The plateau at high pH, not predicted by eq 4, comes about because of a transition from a steady-state situation with respect to the carbanion S^- to one described by fast preequilibrium or fast irreversible formation (depending on relative values of k_{-2} and k_3) and a transition from the rate-determining formation of S^- to its rate-determining decomposition. Where a rapid preequilibrium occurs ($k_{-2} > k_3$)

$$\mathrm{SH} \underset{}{\overset{K_a}{\rightleftharpoons}} \mathrm{S}^- \xrightarrow{k_3} \text{products}$$

and

$$k_{\text{obsd}} = \frac{k_3 K_a}{K_a + a_H} \tag{9}$$

and at high pH $k_{\text{obsd}} = k_3$. Thus

$$k_b = k_3 \tag{10}$$

Where formation of S^- is irreversible ($k_{-2} < k_3$) at high pH, again $k_{\text{obsd}} = k_3$. Note, however, that it is not possible to equate K_a, the dissociation constant of the ester, and K_{a_2} since the latter is purely empirical and describes a portion of the pH–rate profile where a transition from steady state to preequilibrium kinetics is occurring and where the observed kinetics should not be simply first order, *i.e.*, neither of the eq 4 or 9 should apply. K_{a_2} thus has no physical significance but merely defines, in the empirical eq 5, the position of the upper linear portion of the log k_{obsd}–pH curve of slope 1 with respect to the upper plateau (inclusion of a few apparent pseudo-first-order rate constants for the nitrophenol esters in Figure 1 in the transition region discussed above merely reflects the difficulty in picking up deviation from strictly first-order behavior in the results of fast stop-flow experiments at the wavelength routinely used to follow the reactions). A further relationship that can be used is given in eq 11. Solution[16] of the

$$K_a = k_1/k_{-1} = k_2 K_w/k_{-2} \tag{11}$$

five simultaneous equations (6–8, 10, and 11) allows unambiguous definition of all the rate constants of eq 3. These are given for the nitrophenol esters I–III and XI in Table IV.

It is useful at this stage to describe in some detail the typical pH–rate profiles obtained for these hydrolyses in terms of eq 4. The distinctive portions of the log k_{obsd}–pH profile for ester XI in Figure 1 have been designated A to E.

Segment A, as mentioned above, involves the contribution from the usual spontaneous hydrolysis. From eq 4, $k_{\text{obsd}} = k_0$.

Segment B shows a linear dependence of log k_{obsd} on pH of slope +1. If, in eq 4, $a_H > (k_{-2} + k_3)/k_{-1}$ and the third term is negligible because $[HO^-]$ is so small

$$\begin{aligned} k_{\text{obsd}} &= k_1 k_3/k_{-1} a_H \\ &= k_3 K_a/a_H \end{aligned}$$

Hence breakdown of the carbanion is rate determining and no general catalysis of the release of nitrophenol should be observed. Holmquist and Bruice[2a] observed no acetate catalysis in this region for ester II (their extrapolation to zero buffer concentration in this region was valid—see Figure 2). In the present work aniline catalysis of the hydrolysis of XI was observed to fall to zero in this region—see the concluding section.

As the pH rises, a_H falls below $(k_{-2} + k_3)/k_{-1}$ and k_{obsd} tends to a constant value which appears on the profile as segment C

$$\begin{aligned} k_{\text{obsd}} &= k_1 k_3/(k_{-2} + k_3) \\ &= k_1 \end{aligned}$$

when $k_3 \gg k_{-2}$ as for the nitrophenol esters.

Thus there has been a change in the rate-determining step with an increase in pH. Ionization of the ester is now rate determining and general catalysis of this should be seen in rates of nitrophenol release. The presence of such catalysis causes the discrepancy between the present work on ester II and that of Holmquist and Bruice[2a] which was discussed in the previous section. Aniline catalysis is observed here in the hydrolysis of XI.

At higher pH the third term of eq 4, involving $[HO^-]$, becomes important. a_H is still smaller than $(k_{-2} + k_3)/k_{-1}$ of course so that

$$\begin{aligned} k_{\text{obsd}} &= k_2 k_3 [HO^-]/(k_{-2} + k_3) \\ &= k_2 [HO^-] \end{aligned}$$

when $k_3 \gg k_{-2}$. This describes the segment D of the profile. Ionization of the ester is still rate determining and general catalysis has been observed in this region with all the nitrophenol esters of this study.

Finally $k_2[HO^-]$ becomes so large that a transition occurs back to rate-determining breakdown of the carbanion (segment E). For the nitrophenol esters $k_3 > k_{-2}$ so that carbanion formation in this region is essentially irreversible.

The rates of hydrolysis at low pH reflect the acidity of the ester; hence, esters II, III, and XI hydrolyze more rapidly at low pH than ester I since they have larger k_1 and k_2 values and smaller k_{-1} and k_{-2} values. The increasing kinetic and thermodynamic acidity in the series XI > III > I is well known for the α-hydrogens of ketones, thiol esters, and esters, respectively[17] and be-

---

[16] Using pK_w = 13.833, R. A. Robinson and R. H. Stokes, "Electolyte Solutions," Butterworths, London, 1959, p 544.

[17] T. C. Bruice in "Organic Sulphur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 423; G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, 87, 3855 (1965).

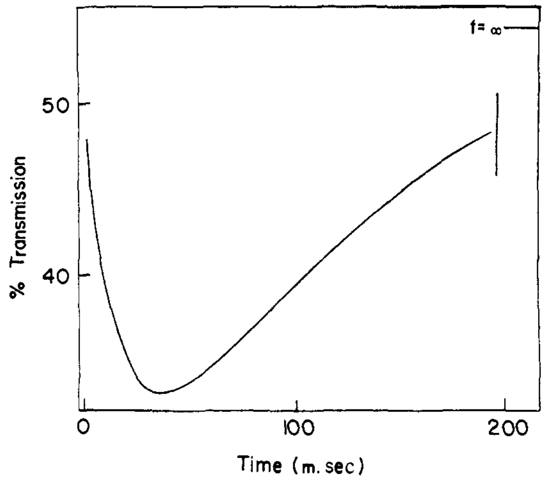


Figure 6. A plot of per cent transmission at 325 nm *vs.* time obtained under stop-flow conditions (mixing time is *ca.* 4 msec) for the hydrolysis of III (0.02 *M* K_2CO_3, pH 9.3). Clearly an A → B → C situation. The properties of B are well in accord with those of the carbanion derived from III. $[B]_{max}$ is 10% $[A]_{t=0}$ and t_{max} is 36 msec. Calculation (see text) gives $[B]_{max} = 7.6\%\ [A]_{t=0}$ and $t_{max} =$ 40 msec. The difference is of course due to carbonate catalysis.

cause inductive effects of the groups –COR, COSR, and CO_2R are similar, is thought to reflect a decreasing contribution of the resonance form $-C(O^-){=}X^+$ in the order CO_2R > COSR > COR.[18] Presumably then in the carbanions, negative charge at the α-C decreases in the order I > III > XI. We were interested to observe the effect of these proposed changes in electron density on the α-C in the carbanion on k_3, but as seen from Table IV, no clear-cut effect appears. Holmquist and Bruice[2b] have shown that an α-cyano group which is thought to be considerably less effective than a carbonyl-containing group in delocalizing charge reduces k_3 from the value found for II by a factor of 10^2. However, the inductive electron-withdrawing power of the cyano group is also greater than that of the acyl substituents so that more work would be useful in this direction to define more closely the effect of the structure of the carbanion on the rate parameters, particularly k_3.

The rate constants of Table IV could be used to predict the details of ester hydrolysis in the "gap" between steady state and equilibrium or irreversible carbanion formation. The hydrolysis of III was examined at pH 8.7–9.7 in Tris, borate, and carbonate buffers at a wavelength of 325 nm (an isosbestic point for the III-*p*-nitrophenoxide system), and using the stop-flow apparatus. The presence of an intermediate was observed (*e.g.*, Figure 6) whose maximum concentration and rates of formation and decomposition were well in accord with those predicted on the basis of the rate constants of Table IV and the known (see Experimental Section) extinction coefficient of the carbanion.

It is interesting to compare the hydrolysis of the ester I with that of the thiol malonate IV. These esters have leaving groups of nearly the same basicity. (Gregory and Bruice[6] report a pK_a of 7.3 for 2,2,2-trifluoroethanethiol.) For the thiol ester, equilibrium carbanion (λ_{max} 280 nm) formation was observed at all pH (above 7). If the ElcB path is operating eq 9 should hold. The same pH–rate profile (Figure 1) should also be seen if the normal BAc2 mechanism is operating.[2b]

$$S^- \underset{}{\overset{K_a}{\rightleftarrows}} SH \xrightarrow{k_{OH}} \text{products}$$

$$k_{obsd} = k_{OH}[K_w/(K_a + a_H)] \qquad (12)$$

The data of Figure 1 give pK_a = 9.84 and $k_3 + k_{OH} \cdot K_w/K_a = 0.2$. The contribution of k_3, *i.e.*, of the ElcB mechanism, is not easy to decide with the data available. Holmquist and Bruice[2b] have decided in favor of an ElcB mechanism for *o*-nitrophenyl cyanoacetate because the observed "k_{OH}" value is some 100 times greater than that expected on the basis of a BAc2 mechanism. A similar analysis can be applied to II[2a] and to I, III, and XI where greater rate enhancements are apparently available *via* the ElcB mechanism. Gregory and Bruice[6] report a k_{OH} value of 1.07 $sec^{-1}M^{-1}$ for 2,2,2-trifluoroethyl thiolacetate. Assuming $\rho^* =$ 2.64 for correlating k_{OH} values of 2,2,2-trifluoroethyl thiolacetates[19] (and using σ^* values tabulated by Leffler and Grunwald[13]) a value of k_{OH} of 40 $sec^{-1}M^{-1}$ can be estimated for IV. The observed "k_{OH}" value is 2000 $sec^{-1}M^{-1}$, *i.e.* an apparent enhancement of 50-fold. In view of the above approximations, it would be rash to decide the extent of ElcB participation on the basis of these figures, but certainly the effect, if any, is not large.

Irrespective of the actual contribution from the ElcB mechanism, however, it is clear that the k_3 value for the 2,2,2-trifluoroethyl thiolmalonate is at least 10^3 times smaller than for the *p*-nitrophenol ester I. Evidence discussed later in this section suggests considerable fission of the bond between the carbonyl group and the leaving group in the transition state for the k_3 step. The difference in k_3 values then would be a direct measure of the leaving group abilities of a phenol and a thiol of the same pK_a.

Gregory and Bruice[6] have studied the reactions of *p*-nitrophenyl acetate and 2,2,2-trifluoroethyl thiolacetate with a series of oxygen and nitrogen nucleophiles and showed that the second-order rate constants for the two esters can be correlated *via* eq 13. This shows that

$$\log k_{p\text{-NPA}} = 1.0 \log k_s + 0.6 \qquad (13)$$

the difference in free energy of activation for reactions of *p*-nitrophenyl acetate and the thiol ester with the same nucleophile is independent of the nucleophile used. The authors suggested that this shows that the transition states for nucleophilic attack on the two esters are similar and do not vary with the nucleophile. The transition states for the reactions of *p*-nitrophenyl acetate with strongly basic oxygen anions certainly resemble those expected for nucleophilic attack (rather than that for breakdown of a tetrahedral intermediate) so that it was concluded for reactions of both esters with the nucleophiles considered that the rate-determining step is nucleophile addition with little bond breaking occurring.

Fersht and Jencks have suggested[20] that the absence of an "element effect" in these reactions merely shows that the two compounds have similar transition states for

---

(18) G. E. Lienhard and Tung-Chia Wang, *J. Amer. Chem. Soc.*, **90**, 3781 (1968).

(19) This value is taken as the same as for *p*-nitrophenyl esters (see later in Discussion). This assumption, as a first approximation, is not unreasonable because of the close similarity between *p*-nitrophenyl acetate and 2,2,2-trifluoroethyl thiolacetate in behavior toward nucleophiles.[6]

(20) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **92**, 5432, 5442 (1970).

the reaction with each individual nucleophile, *i.e.*, there could be a change occurring from a transition state resembling formation of a tetrahedral intermediate to one resembling breakdown of a tetrahedral intermediate which is not reflected in the usual Brønsted type plots. They have obtained a linear plot of the type described above for the reactions of nucleophiles with the acetyl-4-methylpyridinium and 1-acetoxy-4-methoxypyridinium ions. This leads them to conclude that the reaction of *p*-nitrophenoxide with the acetyl-4-methylpyridinium ion involves rate-determining nucleophilic attack. Microscopic reversibility then requires that reaction of 4-methylpyridine with *p*-nitrophenyl acetate involves a transition state resembling rate-determining breakdown of a tetrahedral intermediate. This conclusion seems to directly contradict the earlier one of Gregory and Bruice. (It may be noted here though, that pyridine was not one of the nucleophiles examined by Gregory and Bruice—they obtained k_n values of no nucleophiles of pK_a less than 7 except for the α-effect nucleophile hydroxylamine. The reactivity of pyridines, and tertiary amines in general, with 2,2,2-trifluoroethyl thiolacetate remains open to conjecture and experiment.)

The paradox described by Fersht and Jencks does throw some doubt on the value of the type of plot exemplified by eq 13. Despite this however, the results of the present work do support the original conclusion of Gregory and Bruice *viz.* that for the nucleophiles examined nucleophilic attack is rate determining. The great difference in leaving group ability between the anions of *p*-nitrophenol and 2,2,2-trifluoroethanethiol should certainly be reflected in the reactions of their acetates with nucleophiles if departure of the leaving group is important in the rate-determining step. The mechanisms of these reactions and the E1cB reactions are of course different but leaving group abilities should be essentially common. The "element effect" here then could still be a useful concept.

Acetoacetate Esters. The large dependence of the plateau rate, k_p, on the leaving group for the aryl acetoacetates is well in accord with the E1cB mechanism for the hydrolysis of these esters. The much better correlation of log k_p with σ^- rather than σ would be expected if departure of a phenoxide group was a main feature of the rate-determining step, *i.e.*, if $k_p = k_3$ of the E1cB mechanism. The large ρ^- value of 2.8 can be compared with the value $\rho = 0.8$ for k_{OH} for hydrolysis of aryl acetates *via* a BAc2 mechanism.[21]

The great leaving group dependence of the E1cB mechanism is also seen in Figure 3. The slope of the linear plot of log k_p *vs.* pK_a of the leaving group is -1.29. For the k_{OH} of a series of acetyl esters, Bruice, *et al.*,[22] report the slope of the analogous plot as -0.26.

As mentioned above, the magnitude of observed rate constants for *p*-nitrophenyl acetoacetate (XI) also suggests some special mechanism is operating. From k_{OH} values for *p*-nitrophenyl acetate[23] and *p*-nitrophenyl chloroacetate[24] a ρ^* value of 2.64 can be derived leading to an estimate of 3.8×10^2 sec^{-1} M^{-1} for k_{OH} of XI. The observed value (taken from the upper part of the log k_{obsd}-pH curve of slope +1) is 1.32×10^5, suggesting a rate enhancement *via* the E1cB mechanism of some 350-fold.[25] A similar treatment can be applied to the phenyl ester V where the data of Bruice, *et al.*,[3b] suggest a k_{OH} of 10^2 sec^{-1} M^{-1}. A value of 2×10^3 sec^{-1} M^{-1} was observed, giving an enhancement of only 20-fold in this case. Clearly the effectiveness of the E1cB mechanism with respect to the BAc2 mechanism decreases as the pK_a of the leaving group rises. This, of course, would be expected from the ρ values discussed above.

Only small leaving group dependence was observed for a series of alkyl acetoacetates XII–XIV, XVII (the slope of a plot of log k_p *vs.* pK_a of leaving group (Figure 3) is -0.05). A few measurements with ethyl acetoacetate at lower pH gave, using eq 10, $pK_a = 10.58$, $k_{OH} = 1.13$ sec^{-1} M^{-1}. The former seems a good estimate of the thermodynamic pK_a of the ester under these conditions (Bell[11] reports 10.7 at 25°) and the former is as would be expected on the basis of data available for the BAc2 hydrolysis of ethyl acetates.[26] A similar measurement for propargyl acetoacetate yields $pK_a = 9.83$ and $k_{OH} = 7.5$ sec^{-1} M^{-1}. This suggests a plot of log k_{OH} *vs.* pK_a of leaving group for the alkyl acetoacetates of slope -0.35.

The k_{OH} values and leaving group dependence of the alkyl acetoacetates suggest that a BAc2 mechanism with an inert carbanion applies for these esters. Consequently it appears that a changeover from a BAc2 to an E1cB mechanism occurs as the pK_a of the leaving group falls below 11. The importance of the leaving group in the E1cB mechanism however is such that qualities other than its pK_a control the susceptibility of the ester to E1cB hydrolysis. This point has been mentioned in the comparison of the *p*-nitrophenyl and thiolmalonates I and IV, but even among oxygen esters whose leaving groups have the same pK_a there are apparently distinctions. The oxime ester XVI is more than ten times less reactive than an aryl acetoacetate with the same leaving group pK_a. The extent to which its hydrolysis proceeds by an E1cB mechanism is of course open to question, but its behavior is clearly different from the analogous aryl acetoacetate. For esters hydrolyzing *via* a BAc2 mechanism no such clear distinction of oxime esters seems to occur. The k_p value of the higher pK_a oxime ester XV is close to that expected for the acetoacetate ester of an alcohol of the same pK_a and hydrolyzing mainly *via* a BAc2 mechanism. The k_{OH} value of acetoxime acetate[23] fits on the same log k_{OH} *vs.* pK_a leaving group plot as alkyl and aryl acetates.[22] Qualitatively and quantitatively then, the leaving group is of major importance in the reactions of esters *via* an E1cB mechanism.

Deuterium Solvent Isotope Effects. Tobias and Kézdy[2] have suggested the use of deuterium solvent isotope effects to distinguish between reactive (E1cB) and inert carbanions in ester hydrolyses. They propose

---

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

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

(23) J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 835 (1964).

(24) K. Koehler, R. Skora, and E. H. Cordes, *ibid.*, **88**, 3577 (1966).

(25) This is not a completely fair estimate of the effectiveness of the E1cB path for ester XI. At pH's between 2 and 6 a further enhancement factor of from 10 to 10^2 must be included (see Figure 1) and at high pH the value of k_p is some 10^5 times larger than for a comparable ester with an inert carbanion (see Figure 3, and the discussion of the hydrolysis of the alkyl acetoacetates).

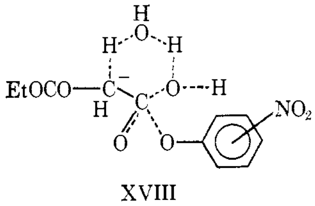
(26) R. P. Bell and A. A. W. Coller, *Trans. Faraday Soc.*, **61**, 1445 (1965); W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, **83**, 1743 (1961).

for the plateau rate k_p, $k_{H_2O}/k_{D_2O} = 1.0$ for an ElcB mechanism and $k_{H_2O}/k_{D_2O} = 1.54$ for a BAc2 mechanism. Their example, 5-nitrocoumaranone, gave an isotope effect of 1.72 from which they concluded the presence of a BAc2 hydrolysis mechanism and an inert carbanion. It was of interest to us to examine the isotope effects of the series of esters available from this study, some of which clearly hydrolyze *via* an ElcB mechanism. The results obtained are in Table III. Also included here are comparable figures for phenyl cyanoacetate, shown by Bruice, *et al.*,[3] to hydrolyze *via* a BAc2 mechanism and with an inert carbanion.

The data of Table III show the general trend predicted by Tobias and Kézdy. The difference between extremes is not as large as predicted; the ratio does not fall as low as 1.0 for esters hydrolyzing *via* the ElcB mechanism (it would not really be expected to because of a small secondary isotope effect arising because of exchange of the second α-H of the ester), nor does it seem to rise as high as 1.5 for the esters hydrolyzing *via* the BAc2 mechanism. There is also apparently some overlap in cases where the ElcB mechanism is less than 100 times as effective as the BAc2 path (esters IV, V, and VI) and distinction between the mechanisms cannot be achieved here on the basis of the solvent isotope effect on k_p. The isotope effect for III is also rather larger than expected.

It would seem then that the deuterium solvent isotope effect used in this way is not a generally applicable criterion for distinguishing ElcB and BAc2 mechanisms in these reactions except perhaps for cases where $k_{H_2O}/k_{D_2O} \leqslant 1.3$; the results of the present work suggest that the latter cases can be taken as ElcB hydrolyses.

The small size of the isotope effect on k_p with the most reactive ElcB esters suggests little solvent participation in the elimination of the leaving group from the carbanion. As a possible alternative to a mechanism involving ketene formation, Bruice and Holmquist[2a] considered a transition state such as XVIII. This now does not seem likely. Their alternate proposal of a transient free ketene intermediate is favored. The amount of solvent participation in the transition state probably increases as the leaving group becomes poorer, as indicated by the isotope effects of the aryl acetoacetates.



XVIII

Trapping the Ketene Intermediate. The effects of buffer species on the kinetics of ElcB ester hydrolyses have been described in detail in the earlier paper from this laboratory.[2a] The main effect is that of catalysis of carbanion formation with a usually smaller term (depending on the buffer) describing direct nucleophilic attack on the ester. The catalysis of carbanion formation is distinguished by saturation kinetics with respect to release of the leaving group observed at high buffer concentration. Such saturation phenomena (plots of k_{obsd} *vs.* buffer concentration curved downwards) were observed with the esters I–III and XI examined in detail in this study. In particular the hydrolysis of XI in aniline buffers was examined. The results are shown in Figure 5. To describe curves of this type the additional terms needed in eq 3 are shown in eq 14. k_4 and k_{-4}

$$\text{products} \xleftarrow{k_5[\text{B}]} \text{SH} \underset{k_{-4}[\text{BH}^+]}{\overset{k_4[\text{B}]}{\rightleftarrows}} \text{S}^- \tag{14}$$

involve general catalysis of the ester ionization and k_5 describes direct nucleophilic attack of the buffer base on the ester carbonyl group, *i.e.*, direct nucleophilic displacement.

Using the steady-state approximation as before eq 15

$$k_{obsd} = k_0 + k_5[\text{B}] + \frac{k_3[k_1 + k_2[\text{OH}] + k_4[\text{B}]]}{k_3 + k_{-1}[\text{H}^+] + k_{-2} + k_{-4}[\text{BH}^+]} \tag{15}$$

can be derived for pseudo-first-order rate constants for phenol release. The best fit to the experimental curves for the hydrolysis of XI in aniline buffers (the solid lines of Figure 4) were obtained using the constants of Table IV, $k_4 = 25\ \text{sec}^{-1}\ M^{-1}$, $k_{-4} = 1.3 \times 10^5\ \text{sec}^{-1}\ M^{-1}$, and $k_5 = 0$. This treatment suggests very little direct nucleophilic displacement of *p*-nitrophenol by aniline.

On the other hand, Figure 5 shows the fraction, f, of acetoacetanilide formed under the same conditions. A curve of this type would be obtained from a kinetic scheme of the type

$$\text{SH} \begin{array}{l} \xrightarrow{k[\text{PhNH}_2]} \text{acetoacetanilide} \\ \xrightarrow{k'[\text{H}_2\text{O}]} \text{other products} \end{array} \tag{16}$$

Then

$$f = \frac{k[\text{PhNH}_2]}{k[\text{PhNH}_2] + k'[\text{H}_2\text{O}]}$$

The solid line of Figure 5 uses $k/k'[\text{H}_2\text{O}] = 130$.

Ignoring for a moment the derivation of eq 15 it is clear that the kinetics of phenol release are incompatible with the product analysis for any one-step mechanism and this even if the catalysis of phenol release did involve direct nucleophilic displacement in some way (the curves arising for example by some complexation phenomenon). For example, at pH 4.1 the amount of anilide formed could not exceed 20% and yet one anilide determination at this pH shows 50% of the ester converted to anilide. Obviously some of the "uncatalyzed" background reaction must be yielding the anilide.

These results show then the presence of a more complex reaction. The phenol release and product formation (acyl transfer) steps are clearly different. The kinetics of phenol release are well in accord with the theory outlined in a previous section, *i.e.*, general catalysis of phenol release in segment C of the pH–rate profile (Figure 1) which disappears at lower pH (segment B) and at high buffer concentration where carbanion breakdown becomes rate determining.

The product formation results are also in accord with an ElcB mechanism. As well as catalyzing carbanion formation (and thus phenol release) the aniline competes with water for attack on an acylating intermediate after phenol release. This intermediate is most logically the transient ketene.

Acknowledgment. This work was supported by a grant from the National Institutes of Health. We would like to thank Professor W. P. Jencks for allowing us to read his manuscript[20] prior to publication.