J. Am. Chem. Soc. **1982**, *104*, 1644-1653

Extended E1cB Mechanism for Ester Hydrolysis: Allylic Substitution via Carbanion in Ester Hydrolysis

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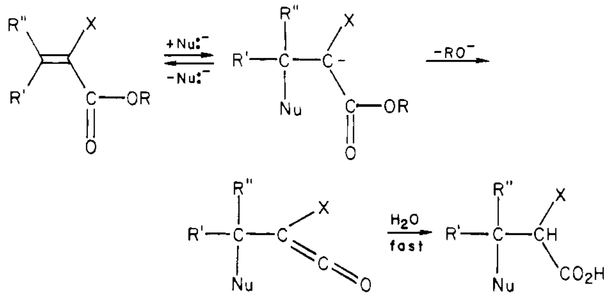
Abstract: Studies of E1cB hydrolysis of esters have been extended to the investigation of ester hydrolysis via allylic substitution (eq 2). The hydrolysis of *p*-nitrophenyl 2-cyano-3-(*p*-methoxyphenyl)propenoate (**1**) provides *p*-nitrophenol (p-NP), 2-cyano-3-(*p*-methoxyphenyl)propenoic acid (**2**), *p*-methoxybenzaldehyde (**6**), and cyanoacetic acid. The percentage yields of the products varied with pH; below pH 8 hydrolysis of **1** occurs predominantly by way of a retro-Knovenagel reaction to yield p-NP and **6**, while above pH 8, the ester hydrolysis of **1** provides **2** and by way of a retro-Knoevenagel reaction **6**. The pH dependence of the two competing processes (ester hydrolysis and retro-Knoevenagel reaction) were provided by a log ($[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$)–pH profile. The rate of hydrolysis of **1** (30 °C) obeys the first-order rate law, and the carbanion (**7**) and carbon acid (**8**) intermediates do not accumulate in the course of hydrolysis. At pH values above 12, two reaction processes, well separated in time, were observed; the initial first-order rate process is associated with the formation of the same products obtained between pH 8 and 12, and the slow reaction is associated with hydrolysis of **2** to **6** and cyanoacetic acid (Scheme V). The mechanism of lyate species hydrolysis of **1** was elucidated by use of log k_{ly} vs. pH and log ($[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$) vs. pH profiles and by comparison of $\Delta S^\ddagger$ and $\Delta S_2^\ddagger - \Delta S_6^\ddagger$ with known literature values. The three mechanisms which may be considered for hydrolysis of **1** involve: (i) competitive and parallel first-order decay of **1** by C–C bond scission to provide **6** + p-NP and ester hydrolysis to provide **2** + p-NP (Scheme II); (ii) addition of HO to the C–C double bond of **1** to provide a carbanion **7** which then undergoes parallel first-order decomposition via C–C bond scission to yield p-NP + **6** and ester hydrolysis through a ketene intermediate to provide p-NP + **2** (Scheme III); and (iii) addition of the elements of $\mathrm{HO^-}$ plus $\mathrm{H^+}$ to the C–C double bond of **1** to yield the carbon acid ester **8** which then partitions to p-NP + **2** and p-NP + **6** (Scheme IV). The reactions of Scheme II do not predict the correct pH dependencies for the two hypothetical parallel reaction paths, which may be determined from the pH dependence of k_{ly} and $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$, nor the values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for ester hydrolysis typical of the $\mathrm{B_{AC}2}$ mechanism required by Scheme II. The sequences of Scheme III predict the observed dependencies of k_{ly}, predict ratios $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$ upon pH, and explain the determined values of $\Delta S^\ddagger{}_2 - \Delta S^\ddagger{}_6$. The mathematical forms of equations derived from the sequences of reactions of Scheme IV are sufficient to fit the log k_{ly} vs. pH and log $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$ vs. pH profiles. However, Scheme IV is strongly disfavored on the basis, among other considerations, that values of the rate constant for the $\mathrm{B_{AC}2}$ hydrolysis of **8** determined by any of the four possible simplifying kinetic assumptions is more than 100-fold greater than values which may be approximated from known kinetic free-energy relationships. Kinetic analysis reveals that the rate-determining steps to product formation for the mechanism of the favored Scheme III cannot be discerned on the basis of the data collected in this study. The hydrolysis of 2-cyano-3-(*p*-methoxyphenyl)propenoic acid (**2**) (→ **9** → **10** → **6**) has been studied, and the mechanism is discussed in terms of the improbability of Scheme IV for hydrolysis of **1**. The conversion of **8** → **1** is an example of the little studied dehydration of an alcohol by way of a carbanion (**7**) intermediate. In this reaction, the $(\mathrm{E1cB})_{\mathrm{anion}}$ mechanism operates at high pH, while at low pH formation of **7** is rate determining and the $(\mathrm{E1cB})_{\mathrm{I}}$ mechanism predominates. Departure of $\mathrm{HO^-}$ from **7** to yield **1** is acid catalyzed. Eliminations of $\mathrm{HO^-}$ and p-NP from **7** to yield **1** and ketene, respectively, represent parallel first-order reactions. The ability of p-NP to compete with $\mathrm{HO^-}$ as a leaving group is attributed to (i) the greater free-energy content of the ketene product and (ii) the conformational restrictions imposed upon E1cB ester hydrolysis.

The E1cB mechanism of carboxylic acid ester hydrolysis was demonstrated in this laboratory in 1969.[1] In the interim, many investigations of this mechanism have been published.[2] Requisites to the E1cB hydrolysis of an ester are a weakly basic leaving group and some stabilization of a negative charge on the carbon atom α to the ester group.[3] Nucleophilic addition to carbon-carbon double bonds which are activated by electron-withdrawing groups is an important elementary process in organic chemistry and one which has received considerable attention in recent years.[4,5] In the reaction of eq 2, a carbanion is generated on the carbon atom α to an ester function by nucleophilic addition to an electron-deficient C–C double bond in the α,β-unsaturated ester. Nucleophilic addition to α,β-unsaturated carboxylic acid esters provides a logical extension to the study of the E1cB mechanism for ester hydrolysis.

$$\mathrm{X{-}CH_2CO_2R} \underset{\Sigma k_{-1}[\mathrm{acid}]}{\overset{\Sigma k_1[\mathrm{base}]}{\rightleftharpoons}} \mathrm{X{-}\overset{-}{C}H{-}CO_2R} \xrightarrow{-\mathrm{RO^-}} \mathrm{X{-}CH{=}C{=}O} \xrightarrow[\text{fast}]{\mathrm{H_2O}} \mathrm{X{-}CH_2{-}CO_2H} \quad (1)$$



(2)

We have chosen *p*-nitrophenyl 2-cyano-3-(*p*-methoxyphenyl)propenoate (**1**) as the principal substrate for this investigation. The choice of **1** has been predicated on the basis of the two

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(1) (a) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993. (b) Holmquist, B.; Bruice, T. C. *Ibid.* **1969**, *91*, 3003.

(2) Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627. Douglas, K. T. "Progress in Bioorganic Chemistry", Kaiser, E. T., Kézdy, F. J., Eds.; Wiley-Interscience: New York, 1976; Vol. 4.

(3) Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956.

(4) (a) Bernasconi, C. F.; Fornarini, S. *J. Am. Chem. Soc.* **1980**, *102*, 5329. (b) Bernasconi, C. F.; Fox, J. P.; Fornarini, S. *Ibid.* **1980**, *102*, 2810. (c) Bernasconi, C. F.; Leonarduzzi, G. D. *Ibid.* **1980**, *102*, 1361. (d) Bernasconi, C. F.; Carrê, D. J. *Ibid.* **1979**, *101*, 2698. (e) Schreiber, B.; Martinek, H.; Wolschann, P.; Schuster, P. *Ibid.* **1979**, *101*, 4708.

(5) For the reviews: (a) Patai, S.; Rappoport, Z. "The Chemistry of Alkenes"; Patai, S., Ed.; Interscience: New York, 1964; p 469. (b) Fyfe, C. A. "The Chemistry of the Hydroxyl Group", Part 1; Patai, S., Ed.; Interscience: New York, 1971; p 51.

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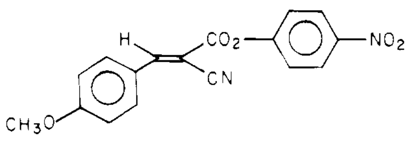

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following considerations: (a) appreciable cis–trans isomerization of the C–C double bond is avoided because the steric requirements for the cyano group are less than the alkoxy- or phenoxycarbonyl group, and thus the isomer in which the cyano and aryl groups are in the cis position is favored; and (b) a *p*-methoxy substituent on the phenyl group was chosen for its potential deterring effect on the fission of the C–C bond which occurs competitively with ester hydrolysis.

Experimental Section

Materials. Reagent grade KCl, K_2CO_3, KH_2PO_4 and CH_3CO_2K were used without purification. Reagent grade pyridine was distilled over CaH_2 and stored in the dark under an N_2 atmosphere. Acetonitrile was of spectroquality. Aqueous solutions were prepared from deionized and freshly double-distilled water.

2-Cyano-3-(*p*-methoxyphenyl)propenoic acid (2), 2-cyano-3-(*p*-methylphenyl)propenoic acid (3), 2-cyano-3-phenylpropenoic acid (4), and 2-cyano-3-(*p*-chlorophenyl)propenoic acid (5) were prepared by the method of Le Moal et al.[6] The melting points were found to agree with literature values (mp 227–229 °C for **2**, 190–192 °C for **3**, 179–180 °C for **4**, and 198–200 °C for **5**).

***p*-Nitrophenyl 2-Cyano-3-(*p*-methoxyphenyl)propenoate (1).** 2-Cyano-3-(*p*-methoxyphenyl)propenoic acid (2.0 g, 6.2 mmol) in 40 mL of benzene was treated with 5.0 mL of trifluoroacetic anhydride[7] at room temperature by stirring for 10 min. Then 3 g of *p*-nitrophenol (p-NP) in 5 mL of benzene was added at once and stirring was continued for 1 h. The reaction mixture was quenched with ice water, carefully neutralized with ice-chilled 1 M KOH solution, washed with water, and dried over magnesium sulfate. After removal of solvents, the crude product was recrystallized twice from a benzene–hexane mixture, mp 178–189 °C.

Kinetic Measurements were carried out in aqueous acetonitrile (50% v/v) at $\mu = 0.17$ (with KCl) and unless otherwise stated at 30 ± 0.1 °C. A Cary 118 spectrophotometer was employed to follow reactions by repetitive scanning and to obtain spectra for product analysis. A Gilford Model 2000, Perkin-Elmer Lambda 3 and Durrum-Gibson Model 13001 stopped-flow spectrophotometers were appropriately used to follow spectral changes at single wavelengths. Reactions carried out under other than stopped-flow conditions were initiated by the addition of 30 μL of stock solution of **1** in acetonitrile to a mixture of 1470 μL of acetonitrile and 1500 μL of aqueous buffer solutions equilibrated at the desired temperature. Acetonitrile stock solutions of **1** were prepared from freshly dried acetonitrile and stored at −20 °C. These stock solutions were employed for a month and then discarded even though the continued use of a stock solution for a much longer time did not alter either kinetic or product analysis results.

Analysis for the products of hydrolysis of **1** were carried out by synthesizing the UV spectrum of the product mixture from the spectra of the individual products. For this purpose, the spectra of each product were determined under the conditions employed for the ester hydrolysis (i.e., solvent, buffers, identical scan time, etc.), and the reaction product spectra were computer generated from the component spectra using the equation:

$$\mathrm{OD}^{l}{}_{\mathrm{syn}} = \sum_{i}^{n} a_i \mathrm{OD}^{l}{}_{i} \qquad (3)$$

where n = number of components and l means the wavelength. The optimized set $a_1, a_2, \ldots, a_n$ (% yield/100 of the component n) was obtained by minimizing the summation of squared deviations, $\sum^m \delta^2$ (where $\delta = \mathrm{OD}^l{}_{\mathrm{syn}} - \mathrm{OD}^l{}_{\mathrm{obsd}}$ and m = the number of data points) between synthesized ($\mathrm{OD}^l{}_{\mathrm{syn}}$) and measured spectra ($\mathrm{OD}^l{}_{\mathrm{obsd}}$) at 2-nm intervals between 250 and 420 nm (86 data points). Actual calculations were carried out by using the equation:

$$(\partial \sum^{m} \delta^2 / \partial a_i)_{a_{j \neq i}} = 0 \qquad (4)$$

The limitation of such procedures is reached when the spectra of products are closely similar. In this study this situation arose with the products 2-cyano-3-(*p*-methoxyphenyl)propenoate (anionic form) and *p*-nitrophenol (acidic form). Therefore, the yields of the products obtained by low-pH hydrolysis were determined as follows. The product solution was brought to pH 12–13 by addition of a few drops of concentrated KOH solution. The UV spectrum of this solution was then computer analyzed as previously described. The change in the spectrum during the second phase of reaction (see following paragraph) was followed, and the yield of **2** formed by the first phase reaction was calculated from the change in absorbance. The yield of **2**, thus calculated, was found to be within the range of 1.1× to 0.85× the yields obtained by the former method.

Table I. Yields of Products[a, b]

pH	% yields			% rel yields		k_{obsd} of 2nd-phase reaction (s^{-1})
	p-NP	**2**	**6**	([**2**] + [**6**])/[*p*-NP]	[**2**]/[**6**]	
11.61	98.6	77.7	22.2	101.3	3.50	
11.67	102.5	81.1	23.5	102.0	3.45	
12.62	100.4	80.1	22.2	101.9	3.61	
12.59	100.2	80.4	18.1	98.3	4.44	
13.03	101.3	81.3	18.7	98.7	4.35	
13.60[c]	83.2	70.8	11.8	99.2	6.00	4.62×10^{-5}
13.90[c]	92.3	79.7	12.0	99.3	6.64	1.13×10^{-4}
14.06[c]	93.2	81.2	11.0	98.9	7.38	2.22×10^{-4}

[a] Typical but not selected results are given to show the accuracy of the product analysis method. [b] Experiments in this table were carried out in 50% aqueous acetonitrile, potassium hydroxide as a buffer ($\mu = 0.16$ with KCl at 30 °C). [c] These results are obtained by using the corrected spectrum to avoid the influence of second-phase reaction (see text).

In the case of product analysis of hydrolytic reactions at high pH, a correction was required because the carboxylic acid **2** obtained from ester **1** is itself hydrolyzed. The general experimental procedure employed and the means for correction are as follows. To the prethermostated buffer solution was added a known volume of the stock solution of **1**. The reaction solution was mixed and its spectrum immediately determined (initial spectrum). During the time required for mixing of the solution and placement in the spectrophotometer, the hydrolysis of **1** was completed. The ensuing hydrolysis of **2** was followed at 324 nm ($\lambda_{\max}$ of **2**). When the hydrolysis of **2** had gone to completion, the spectrum of the reaction solution was taken (final spectrum). Equation 5 was then used

$$\mathrm{OD}^{l}{}_{0} = (\mathrm{OD}^{l}{}_{i} - \mathrm{OD}^{l}{}_{\infty}) \exp(-kt_i) + \mathrm{OD}^{l}{}_{\infty} \qquad (5)$$

to correct the initial spectrum for any change due to hydrolysis of **2**. For eq 5, $\mathrm{OD}^l{}_0$, $\mathrm{OD}^l{}_i$, and $\mathrm{OD}^l{}_\infty$ represent the optical densities of the corrected, initial, and final spectra, respectively, each at l nm. The constant k of eq 5 represents the determined pseudo-first-order rate constant for the hydrolysis of **2**, while t_i is the period of time lapsed between the addition of **1** and the time of scanning at l nm of the initial spectrum. The corrected spectrum of products formed on hydrolysis of **1** was then subjected to the product analysis program mentioned above. The accuracy of this product analysis method was shown by the finding that the sum of the yield of *p*-methoxybenzaldehyde (**6**) and 2-cyano-3-(*p*-methoxyphenyl)propenoic acid (**2**) equaled (±2%) the yield of *p*-nitrophenol which was in the range of 85 to 105% based on **1** used (see Table I).

Results

The following general observations can be made on the hydrolysis of **1**. At pH values below 8, the slow decrease in the absorbance of **1** (353 nm) is associated with an increase in the absorbances of *p*-methoxybenzaldehyde (**6**) (283 nm) and *p*-nitrophenoxide anion (402 nm) and/or *p*-nitrophenol with clear isosbestic points (for example, at pH 7.34: 242, 314, 257, and 231 nm). Between pH 8 and 12 the formation of *p*-nitrophenoxide ion is accompanied by the formation of **6** and 2-cyano-3-(*p*-methoxyphenyl)propenoic acid (**2**) (324 nm). In this pH range the acid **2** is stable. As at the lower pH values, repetitive spectral scanning provided tight isosbestic points; all spectra taken during the course of reaction until completion of reactions could be computer synthesized from the respective spectra of **1**, **6**, p-NP, and **2**. No evidence could be gained for the accumulation of **7** or **8** which, if present, must exist at steady state. Above pH 12 there are observed two reactions which are well separated in time. The more rapid reaction is identical with that observed between

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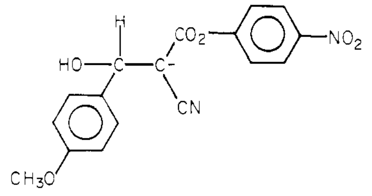
(6) Le Moal, H.; Carrié, R.; Foucaud, A.; Danion-Bougot, R.; Gadreau, C. *Bull. Soc. Chim. Fr.* **1968**, 2156.

(7) Paris, R. C.; Stock, L. M. *J. Org. Chem.* **1965**, *30*, 927.



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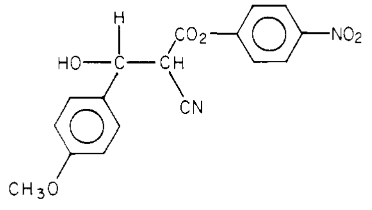

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pH 8 and 12, while the slower reaction represents the formation of **6** and cyanoacetate by the retro-Knoevenagel breakdown of **2**. This second reaction is found to be identical in its time dependences and spectral changes with those observed for the solvolysis of authentic **2** (Scheme I).

All hydrolytic reactions were followed at constant pH at total buffer concentrations >> [**1**] and were found to obey the first-order rate law. Some small contribution to the rate of disappearance of **1** was made by the buffers employed.

$$k_{obsd} = k_{ly} + k_{buff}[\text{total buffer}] \qquad (6)$$

The values of the rate constants for lyate species catalysis (k_{ly}) were obtained from the intercepts of plots of the determined pseudo-first-order rate constant (k_{obsd}) vs. [total buffer] at each constant pH. The values of k_{buff}, obtained as the slopes of these plots, were considered to be of little use because the slope values were quite small as compared with k_{ly} (Figure 1). The rate constants k_{ly} were determined at a number of temperatures. From Arrhenius plots (Figure 1) the activation parameters at pH 8.18 were calculated (30 °C) to be $\Delta H^{\ddagger} = 20.0 \pm 0.4$ kcal mol^{-1} and $\Delta S^{\ddagger} = -12.6 \pm 1.4$ eu, and at pH 12.04, $\Delta H^{\ddagger} = 12.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -11.6$ eu.

The pH–log k_{ly} profile for solvolysis of 1 is presented in Figure 2. The points are experimental, and the line used to fit the points was computer generated from the empirical equation

$$k_{ly} = k_{1e} + \frac{k_{2e}K_{3e}}{K_{3e} + a_H} + \frac{k_{4e}K_{5e}}{K_{5e} + a_H} \qquad (7)$$

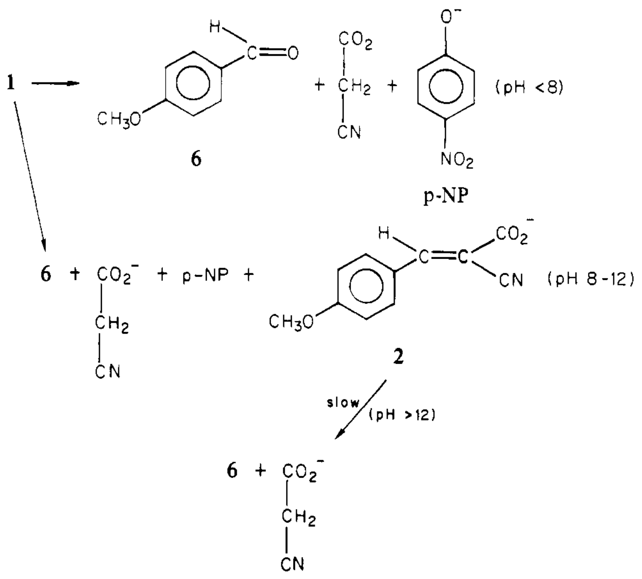
The means for the determination of the reaction products is described in the Experimental Section. The log ([**2**]$_\infty$/[**6**]$_\infty$) vs. pH profile is presented in Figure 3. The points of Figure 3 are experimental and the line fitting the points was computer generated from eq 8. The product ratios plotted in Figure 3 were obtained

$$\frac{[\mathbf{2}]_\infty}{[\mathbf{6}]_\infty} = A_1 + \frac{A_2}{A_3 + a_H} + \frac{A_4}{a_H} \qquad (8)$$

by determining [**2**]$_\infty$/[**6**]$_\infty$ at various buffer concentrations and extrapolating to zero buffer concentration. There is no theoretical reason why plots of [**2**]$_\infty$/[**6**]$_\infty$ vs. [total buffer] should be linear, but they appear to be with the phosphate and pyridine buffers employed. From a plot of log ([**2**]$_\infty$/[**6**]$_\infty$) vs. $1/T$ (K) at pH 8.18 (Figure 4), the following relative activation parameters were determined: $\Delta H_2^{\ddagger} - \Delta H_6^{\ddagger} = 8.3 \pm 0.5$ kcal mol^{-1} and $\Delta S_2^{\ddagger} - \Delta S_6^{\ddagger} = 23.7 \pm 1.8$ eu.

A retro-Knoevenagel reaction of 3-aryl-2-cyanopropenoic acids is observed at high pH values (Scheme I for **2**). The rate constants and conditions of kinetic investigation are provided in Table II.

Scheme I



Scheme II

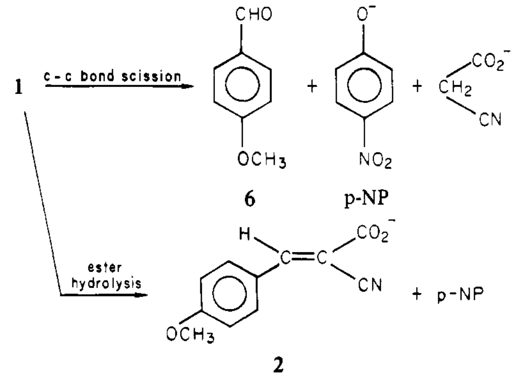
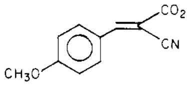
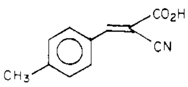
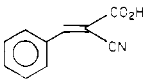
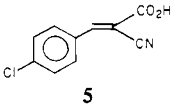


Table II. Hydrolysis of 3-Aryl-2-cyanopropenoic Acids at 30 °C

compound	solvent (AN-H_2O)	pH range	no. of data pts	k^{OH}, M^{-1} s^{-1}
 **2**	1:1^a 1:100^b	12.68–14.00 12.66–13.61	5 8	7.21×10^{-3} ^{c} 1.17×10^{-2} $^{d-f}$
 **3**	1:100^b	11.68–13.63	10	1.88×10^{-2} $^{d-f}$
 **4**	1:100^b	10.85–13.64	11	3.26×10^{-2} ^{d,f}
 **5**	1:100^b	10.74–13.58	12	6.18×10^{-2} ^{d,f}

[a] $\mu = 0.17$ with KCl. [b] $\mu = 1.0$ with KCl. [c] Calculated on the basis of pK_W = 15.6; see ref 20. [d] Calculated on the basis of pK_W = 13.83; [R. A. Robinson and R. H. Stokes, "Electrolyte Solutions", Butterworths, London, 1959, p 544]. [e] Activation parameters are as follows: $\Delta H^{\ddagger} = 13.5$ kcal mol^{-1}, $\Delta S^{\ddagger} = -22.9$ eu at 30 °C calculated from nine data points in the temperature range of 1.0–47.0 °C. [f] $\rho = 1.42$ ($r = 0.994$).

Discussion

A discussion of the experimental results is best initiated by a consideration of the plausible mechanisms for the hydrolysis of **1** which are presented in Schemes II, III, and IV. The three schemes differ in the assumption that ester hydrolysis and the C–C bond scission in the retro-Knoevenagel condensation do not possess a common intermediate (Scheme II) or possess, as common in-

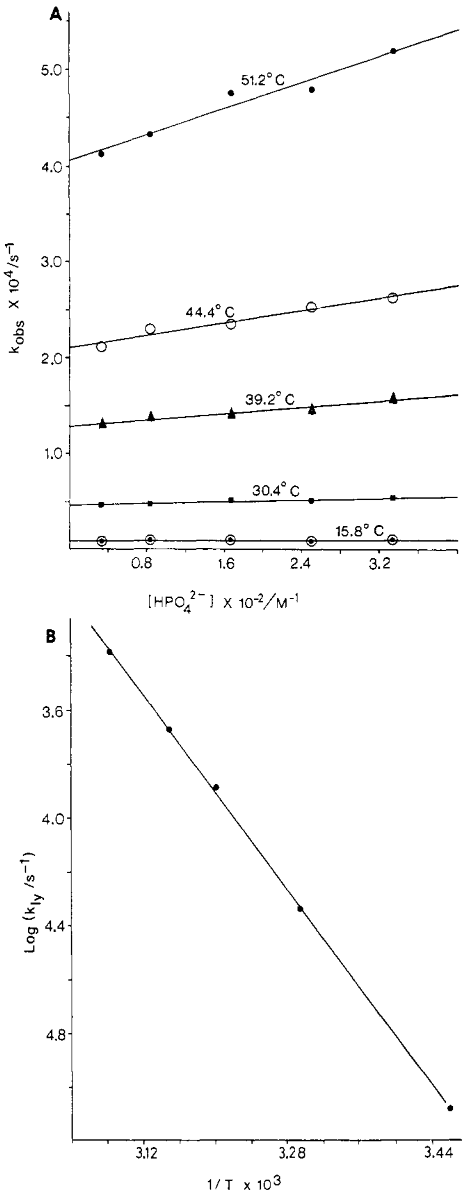
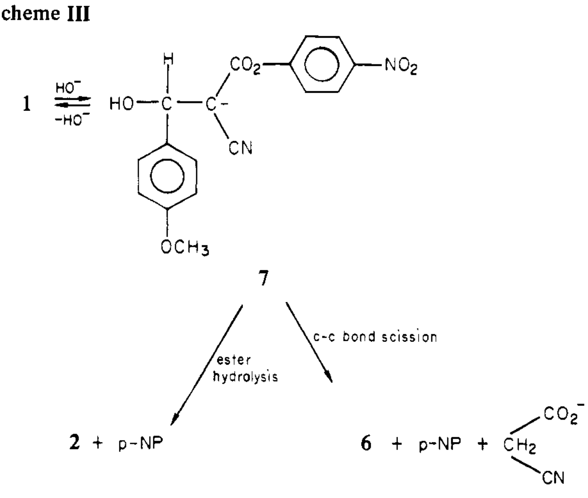


Figure 1. (A) Plots of the pseudo-first-order rate constant (k_{obsd}) vs. [HPO_4^{2-}] and (B) Arrhenius plot of k_{ly}, both for hydrolysis of *p*-nitrophenyl 2-cyano-3-(*p*-methoxyphenyl)propenoate (**1**) at pH 8.18.

Scheme III



termediates, the carbanion **7** (Scheme III) or **7** and the carbon acid **8** (Scheme IV).

If the *mechanisms of Scheme II* were operative, then the products of C–C bond scission and ester hydrolysis arise from parallel and competing pseudo-first-order reactions. The rate constants k_{ly} would then be the sum of the pseudo-first-order rate constants for C–C bond breaking (k_c) and ester hydrolysis (k_e) and the ratio of k_e/k_c is obtained from the ratio of $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$ (eq 9). By the use of these relationships, k_c and k_e were determined

$$k_{ly} = k_c + k_e \text{ and } k_e/k_c = [\mathbf{2}]_\infty/[\mathbf{6}]_\infty \qquad (9)$$

as a function of pH (Figure 5). With the exception of the slight sigmoidal curvature near pH 7, the plot of log k_e vs. pH is of slope 1.0, indicating that ester hydrolysis is first order in [HO⁻] between pH 5 and 13. Above pH 13, log k_e gains an independence of pH. In the context of the mechanism of Scheme II, the plateau in the log k_e vs. pH profile at high pH could not be explained since hydrolysis could occur only via a $B_{AC}2$ mechanism and **1** per se possesses no ionizable group. By employing the relationship of

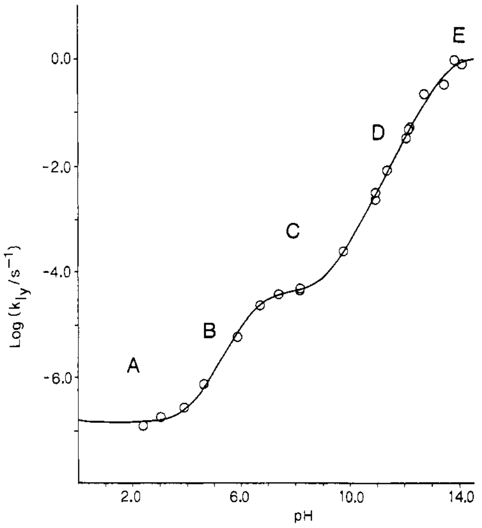


Figure 2. pH–log k_{ly} profile for the lyate species catalyzed hydrolysis of the ester **1**. The points are experimental and the line theoretical, being derived from eq 7; $k_{1e} = 1.47 \times 10^{-7}$ s^{-1}, $k_{2e} = 4.04 \times 10^{-5}$ s^{-1}, $K_{3e} = 2.86 \times 10^{-7}$ M, $k_{4e} = 1.07$ s^{-1}, $K_{4e} = 3.43 \times 10^{-14}$ M.

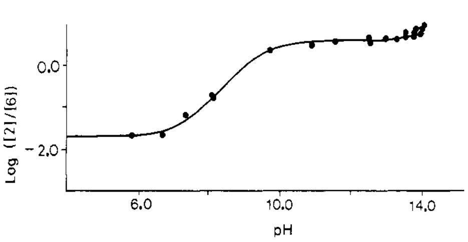
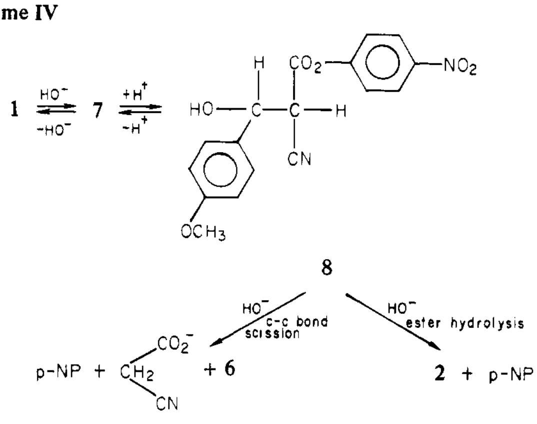


Figure 3. pH–log ([**2**]/[**6**]) profile for the lyate species catalyzed hydrolysis of the ester **1**. The points are experimental and the line is theoretical, being derived from eq 8; $A_1 = 1.97 \times 10^{-2}$ M; $A_2 = 1.10 \times 10^{-9}$ M; $A_3 = 3.01 \times 10^{-10}$ M; $A_4 = 2.94 \times 10^{-14}$ M.

Scheme IV



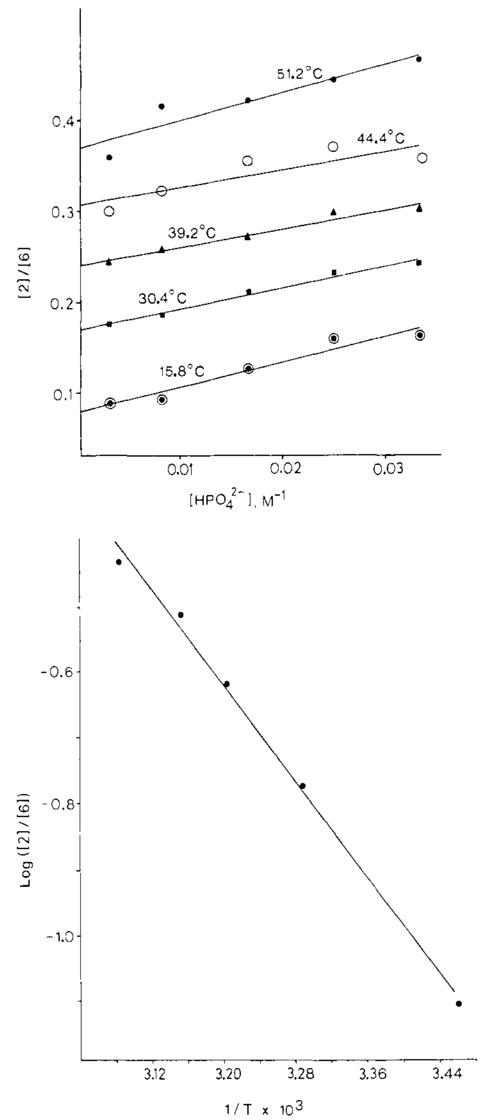
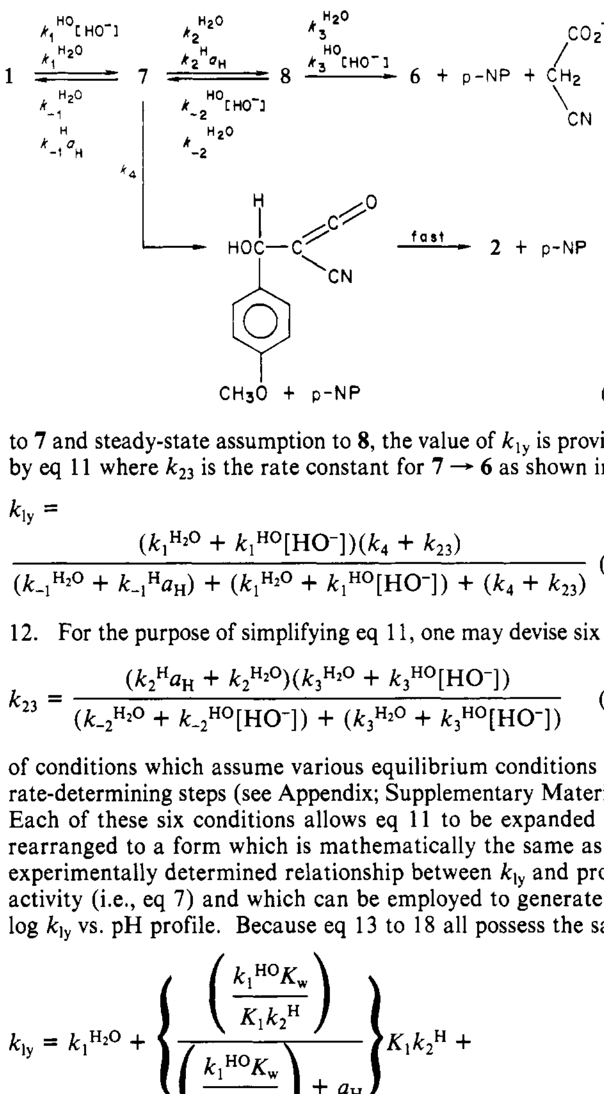


Figure 4. (A) Plots of product ratio [**2**]/[**6**] vs. buffer base concentration for hydrolysis of **1** at pH 8.18 and (B) Arrhenius-type plot of the product ratio [**2**]/[**6**] for the lyate species catalyzed hydrolysis of the ester **1** at pH 8.18.

eq 9 and the k_{ly} constants determined at various temperatures, there may be constructed Arrhenius plots for k_c and k_e (Figure 5). The activation parameters calculated in this fashion are for ester hydrolysis ($\Delta H^\ddagger = 26.9 \pm 1.0$ kcal mol^{-1} and $\Delta S^\ddagger = 6.0 \pm 3.1$ eu) and for C–C bond breaking ($\Delta H^\ddagger = 18.7 \pm 0.5$ kcal mol^{-1} and $\Delta S^\ddagger = -17.1 \pm 1.7$ eu). The value of $\Delta S^\ddagger$ for ester hydrolysis, thus calculated, is positive whereas $\Delta S^\ddagger$ for $B_{AC}2$ ester hydrolysis have been shown to have large negative values. Thus, Tommila and Hinshelwood[8] reported $\Delta S^\ddagger = -19.4$ eu for the alkaline hydrolysis of *p*-nitrophenyl acetate (60% acetate–H_2O v/v at 25 °C) and Jones and Watkinson[9] reported a value of $\Delta S^\ddagger = -14.8$ eu for the alkaline hydrolysis of ethyl *trans*-cinnamate (85.4% ethanol–H_2O v/v at 25 °C). We may conclude on the basis of the log k_e vs. pH profile and the value of $\Delta S^\ddagger$ that Scheme II does not serve to explain the experimental results.



(10)

The mechanisms of Scheme III would most reasonably represent a competition between a retro-Knoevenagel reaction and an ester hydrolysis via a ketene intermediate as shown in eq 10. Applying the "improved steady-state" method of McDaniel and Smoot[10] to **7** and steady-state assumption to **8**, the value of k_{ly} is provided by eq 11 where k_{23} is the rate constant for **7** → **6** as shown in eq 12.

$$k_{ly} = \frac{(k_1^{H_2O} + k_1^{HO}[HO^-])(k_4 + k_{23})}{(k_{-1}^{H_2O} + k_{-1}^{H}a_H) + (k_1^{H_2O} + k_1^{HO}[HO^-]) + (k_4 + k_{23})} \quad (11)$$

For the purpose of simplifying eq 11, one may devise six sets

$$k_{23} = \frac{(k_2^{H}a_H + k_2^{H_2O})(k_3^{H_2O} + k_3^{HO}[HO^-])}{(k_{-2}^{H_2O} + k_{-2}^{HO}[HO^-]) + (k_3^{H_2O} + k_3^{HO}[HO^-])} \quad (12)$$

of conditions which assume various equilibrium conditions and rate-determining steps (see Appendix; Supplementary Material). Each of these six conditions allows eq 11 to be expanded and rearranged to a form which is mathematically the same as the experimentally determined relationship between k_{ly} and proton activity (i.e., eq 7) and which can be employed to generate the log k_{ly} vs. pH profile. Because eq 13 to 18 all possess the same

$$k_{ly} = k_1^{H_2O} + \left\{ \frac{\left(\dfrac{k_1^{HO}K_w}{K_1k_2^{H}} \right)}{\left(\dfrac{k_1^{HO}K_w}{K_1k_2^{H}} \right) + a_H} \right\} K_1k_2^{H} + \left(\frac{K_1}{K_1 + a_H} \right)(k_4 + k_2^{H_2O}) \quad (13)$$

$$k_{ly} = K_1k_2^{H} + \left\{ \frac{\left(\dfrac{K_1(k_4 + k_2^{H_2O}}{k_1^{H_2O}} \right)}{\left(\dfrac{K_1(k_4 + k_2^{H_2O})}{k_1^{H_2O}} \right) + a_H} \right\} k_1^{H_2O} + \left\{ \frac{\left(\dfrac{k_1^{HO}K_w}{k_4 + k_2^{H_2O}} \right)}{\left(\dfrac{k_1^{HO}K_w}{k_4 + k_2^{H_2O}} \right) + a_H} \right\} (k_4 + k_2^{H_2O}) \quad (14)$$

$$k_{ly} = k_1^{H_2O} + \left\{ \frac{\left(\dfrac{k_1^{HO}K_2K_w}{K_1k_3^{H_2O}} \right)}{\left(\dfrac{k_1^{HO}K_2K_w}{K_1k_3^{H_2O}} \right) + a_H} \right\} \frac{K_1k_3^{H_2O}}{K_2} + \left(\frac{K_1}{K_1 + a_H} \right)\left(k_4 + \frac{k_3^{HO}K_w}{K_2} \right) \quad (15)$$

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(8) Tommila, E.; Hinshelwood, C. N. *J. Chem. Soc.* **1938**, 1801.

(9) Jones, B.; Watkinson, J. G. *J. Chem. Soc.* **1958**, 4064.

(10) McDaniel, D. H.; Smoot, C. R. *J. Phys. Chem.* **1956**, *60*, 966.

$$k_{ly} = \frac{K_1k_3^{H_2O}}{K_2} + \left\{\frac{\left(\frac{K_1(k_4 + k_3^{HO}K_w/K_2)}{k_1^{H_2O}}\right)}{\left(\frac{K_1(k_4 + k_3^{HO}K_w/K_2)}{k_1^{H_2O}}\right) + a_H}\right\}k_1^{H_2O} + \left\{\frac{\left(\frac{k_1^{OH}K_w}{k_4 + k_3^{OH}K_w/K_2}\right)}{\left(\frac{k_1^{OH}K_w}{k_4 + k_3^{OH}K_w/K_2}\right) + a_H}\right\}\left(k_4 + \frac{k_3^{HO}K_w}{K_2}\right) \quad (16)$$

$$k_{ly} = \frac{K_1k_3^{H_2O}}{K_2} + \left\{\frac{\left(\frac{k_3^{HO}K_w}{k_2^{H}K_2}\right)}{\left(\frac{k_3^{HO}K_w}{k_2^{H}K_2}\right) + a_H}\right\}K_1k_2^{H} + \left(\frac{K_1}{K_1 + a_H}\right)(k_4 + k_2^{H_2O}) \quad (17)$$

$$k_{ly} = K_1k_2^{H} + \left\{\frac{\left(\frac{k_2^{H_2O}K_2}{k_3^{H_2O}}\right)}{\left(\frac{k_2^{H_2O}K_2}{k_3^{H_2O}}\right) + a_H}\right\}\frac{K_1k_3^{H_2O}}{K_2} + \left(\frac{K_1}{K_1 + a_H}\right)\left(k_4 + \frac{k_3^{HO}K_w}{K_2}\right) \quad (18)$$

mathematical form, each of the six sets of assumptions is kinetically feasible and may not be distinguished on the basis of kinetic studies nor the determined product ratios (vide infra). For this reason, it is not possible to discern the rate-determining step(s) of eq 10.

The product ratio for the reaction sequence of eq 10 is provided by eq 19. The expanded equation for the product ratio, $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$,

$$[\mathbf{2}]_\infty/[\mathbf{6}]_\infty = k_4/k_{23} \quad (19)$$

at all but the highest pH regions is given as eq 20. Comparison

$$\frac{[\mathbf{2}]_\infty}{[\mathbf{6}]_\infty} = \frac{K_2k_4}{k_3^{HO}K_w}\left\{\frac{\left(\frac{k_3^{HO}K_w}{k_3^{H_2O}}\right)}{\left(\frac{k_3^{HO}K_w}{k_3^{H_2O}}\right) + a_H}\right\} + \frac{k_4}{k_2^{H_2O}}\left\{\frac{\left(\frac{k_2^{H_2O}}{k_2^{H}}\right)}{\left(\frac{k_2^{H_2O}}{k_2^{H}}\right) + a_H}\right\} \quad (20)$$

of eq 20 with the experimentally derived equation for $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$ (i.e., eq 8) reveals that one of the following two situations would prevail. In the pH range employed, (i) $k_3^{HO}K_w/k_3^{H_2O} > a_H$ (eq 21), or (ii) $k_2^{H_2O}/k_2^{H} > a_H$ (eq 22). Thus, the lower and upper

$$\frac{[\mathbf{2}]_\infty}{[\mathbf{6}]_\infty} = \frac{K_2k_4}{k_3^{HO}K_w} + \frac{k_4}{k_2^{H_2O}}\left\{\frac{(k_2^{H_2O}/k_2^{H})}{(k_2^{H_2O}/k_2^{H}) + a_H}\right\} \quad (21)$$

$$\frac{[\mathbf{2}]_\infty}{[\mathbf{6}]_\infty} = \frac{k_4}{k_2^{H_2O}} + \frac{K_2k_4}{k_3^{HO}K_w}\left\{\frac{\left(\frac{k_3^{HO}K_w}{k_3^{H_2O}}\right)}{\left(\frac{k_3^{HO}K_w}{k_3^{H_2O}}\right) + a_H}\right\} \quad (22)$$

plateaus in the plot of log $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$ are represented by $k_4/k_2^{H_2O}$ and $K_2k_4/k_3^{HO}K_w$ while the pH dependence of the transition from lower to upper plateaus is given by either $k_4/k_2^{H}a_H$ or $k_4K_2/k_3^{H_2O}a_H$. There are no obvious means of differentiating between the two possibilities.

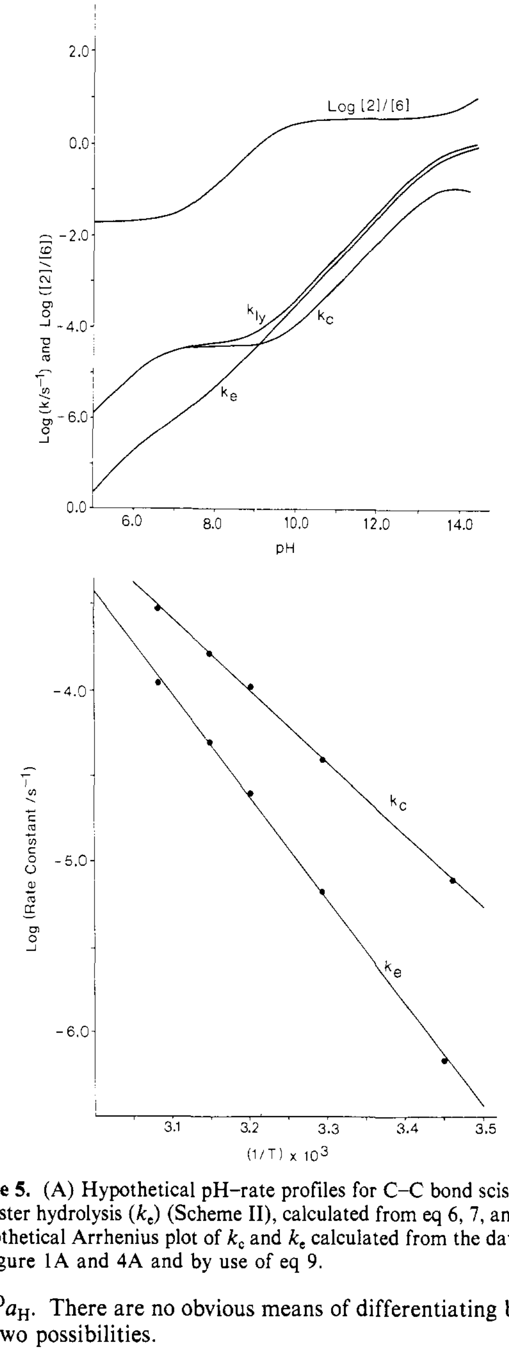
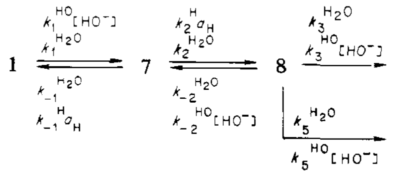


Figure 5. (A) Hypothetical pH-rate profiles for C–C bond scission (k_c) and ester hydrolysis (k_e) (Scheme II), calculated from eq 6, 7, and 9. (B) Hypothetical Arrhenius plot of k_c and k_e calculated from the data shown in Figure 1A and 4A and by use of eq 9.

It has been reported that E1cB ester hydrolysis has a positive activation entropy, as is well anticipated by the fact that the ketene formation from a carbanion precursor is a dissociative process. For example, activation entropies of E1cB alkaline hydrolyses of phenyl *N*-phenylcarbamate[11] and *N*-acetyl-*S*-acetoacetylcystineamine ($CH_3COCH_2COSCH_2CH_2NHAc$)[12] are 5.0 and 10.4 eu, respectively. Therefore, the relative activation parameters, $\Delta S_2^\ddagger - \Delta S_6^\ddagger = 23.7 \pm 1.8$ eu, strongly supports the mechanisms of Scheme III.

The mechanism of Scheme IV will now be considered (eq 23).



(23)

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(11) Christenson, I. *Acta Chem. Scand.* **1964**, *18*, 904.

(12) Douglas, K. T.; Yaggi, N. F. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1037.

Steady-state assumptions in **7** and **8** provide eq 24 where k_{235} is

$$k_{\mathrm{ly}} = \frac{(k_1^{\mathrm{HO}}[\mathrm{HO}^-] + k_1^{\mathrm{H_2O}})k_{235}}{(k_{-1}^{\mathrm{H_2O}} + k_{-1}a_{\mathrm{H}}) + k_{235}} \tag{24}$$

given by eq 25 and k_{3+5} by eq 26. Rearrangement of eq 24

$$k_{235} = \frac{(k_2^{\mathrm{H}}a_{\mathrm{H}} + k_2^{\mathrm{H_2O}})k_{3+5}}{(k_{-2}^{\mathrm{H_2O}} + k_{-2}^{\mathrm{HO}}[\mathrm{HO}^-]) + k_{3+5}} \tag{25}$$

$$k_{3+5} = (k_3^{\mathrm{HO}} + k_5^{\mathrm{HO}})[\mathrm{HO}^-] + (k_3^{\mathrm{H_2O}} + k_5^{\mathrm{H_2O}}) \tag{26}$$

provides eq 27. The combination of any two of the three terms

$$1/k_{1\mathrm{y}} = \underset{\mathrm{I}}{\frac{a_{\mathrm{H}}}{k_1^{\mathrm{HO}}K_{\mathrm{W}} + k_1^{\mathrm{H_2O}}a_{\mathrm{H}}}} + \underset{\mathrm{II}}{\frac{a_{\mathrm{H}}}{K_1(k_2^{\mathrm{H}}a_{\mathrm{H}} + k_2^{\mathrm{H_2O}}}} + \underset{\mathrm{III}}{\frac{a_{\mathrm{H}}}{\frac{K_1}{K_2}\left\{(k_3^{\mathrm{H_2O}} + k_5^{\mathrm{H_2O}})a_{\mathrm{H}} + (k_3^{\mathrm{HO}} + k_5^{\mathrm{HO}})\right\}}} \tag{27}$$

(i.e., I, II, or III) suffices to describe the log k_{ly} vs. pH profile for hydrolysis of **1** (Figure 2). The magnitude of the I, II, and III terms of eq 27 would provide the rate-limiting step if Scheme IV is correct. Thus, if I were to be the numerically largest among the three terms, then nucleophilic addition (i.e., **1** → **7**) would be rate determining. In like manner, if II were the largest, then the proton transfer in **7** → **8** would be rate determining, and C–C bond breaking in **8** → **6** or ester hydrolysis in **8** → **2** would be rate determining if III were to be the largest term. Inspection of eq 23 provides eq 28 for the pH dependence of the product ratio

$$\frac{[\mathbf{2}]_\infty}{[\mathbf{6}]_\infty} = \frac{k_3^{\mathrm{HO}}K_{\mathrm{w}} + k_3^{\mathrm{H_2O}}a_{\mathrm{H}}}{k_5^{\mathrm{HO}}K_{\mathrm{w}} + k_5^{\mathrm{H_2O}}a_{\mathrm{H}}} \tag{28}$$

$[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$. Comparison of eq 28 with the experimentally derived (empirical) equation (eq 8) which fits the plot of log ($[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$) vs. pH (Figure 3) establishes that the plateau at low pH would equal $k_3^{\mathrm{H_2O}}/k_5^{\mathrm{H_2O}}$, the plateau at higher pH equals $k_3^{\mathrm{HO}}/k_5^{\mathrm{HO}}$, and the profile connecting the high and low plateaus is given by $k_3^{\mathrm{HO}}K_{\mathrm{w}}/k_5^{\mathrm{H_2O}}a_{\mathrm{H}}$. These considerations establish that Scheme IV suffices to explain the results of both kinetic and product studies. If Scheme IV (i.e., eq 23) were correct, the differentiation of the rate-determining step (terms I, II, or III) could not be made (just as in the case of Scheme III, eq 10). However, step **8** → **2** or **8** → **6** (term III) cannot be the rate-determining step at low pH because the relation between $k_{3+5}^{\mathrm{H_2O}}$ and $k_{3+5}^{\mathrm{HO}}K_{\mathrm{w}}$, determined by the product ratio, is inconsistent with the relation determined by segments A and B of the log k_{ly} vs. pH profile. Then one may assume, in turn, that the rate-determining steps at low pH are **1** → **7** (term I of eq 27) and **7** → **8** (term II). There remain four possibilities (cases A, B, C, and D) to be considered. Each of these situations may then be analyzed in order to determine if they are reasonable.

Case A. If terms I and II of eq 27 are the largest (i.e., important) and if nucleophilic addition is rate determining (I > II) at low pH, segment A of the log k_{ly} vs. pH profile equals $k_1^{\mathrm{H_2O}}$ ($=1.5 \times 10^{-7}$ s^{-1}) and segment B equals $k_1^{\mathrm{HO}}K_{\mathrm{w}}/a_{\mathrm{H}}$ ($k_1^{\mathrm{HO}} = 1.2 \times 10^{-11}/K_{\mathrm{w}}$ M^{-1} s^{-1}). With increase in pH, protonation of **7** becomes rate determining and segment C equals $K_1k_2^{\mathrm{H}}$ ($K_1 = 3.4 \times 10^{-14}$ M, $k_2^{\mathrm{H}} = 1.2 \times 10^9$ M^{-1} s^{-1}) and segment D equals $K_1k_2^{\mathrm{H_2O}}/a_{\mathrm{H}}$ ($k_2^{\mathrm{H_2O}} = 1.1$ s^{-1}). The value of $k_{3+5}^{\mathrm{HO}}K_{\mathrm{w}}$ would be $>1.1K_2$. In Scheme III, segment E must arise from a breakdown in the steady-state conditions.

Case B. The terms I and III are the largest terms in eq 27 with I > III at low pH. Segments A and B result from rate-determining nucleophilic attack of $\mathrm{H_2O}$ and $\mathrm{HO^-}$, respectively, while segments C and D would result from conversion of **8** to products catalyzed by $\mathrm{H_2O}$ and $\mathrm{HO^-}$, respectively. Again, segment E results from a breakdown of steady-state conditions. In this instance, the calculated constants would be $k_1^{\mathrm{H_2O}} = 1.5 \times 10^{-7}$ s^{-1}, $k_1^{\mathrm{HO}}K_{\mathrm{w}} = 1.2 \times 10^{-11}$ s^{-1}, $K_1 = 3.4 \times 10^{-14}$ M, $k_{3+5}^{\mathrm{H_2O}} = 1.2 \times 10^9K_2$ s^{-1}, and $k_{3+5}^{\mathrm{HO}}K_{\mathrm{w}} = 1.1K_2$ s^{-1}.

Case C. Terms I and II are the largest (i.e., involved) and at low pH II > I. In this instance segment A of the profile represents rate-determining protonation of **7** by $\mathrm{H_3O^+}$; segment B, rate-determining protonation of **7** by $\mathrm{H_2O}$; segment C, rate-determining nucleophilic attack of $\mathrm{H_2O}$ upon **1**; and segment D, nucleophilic attack of $\mathrm{HO^-}$ upon **1**. For this case, the constants may be calculated to be $k_1^{\mathrm{H_2O}} = 4.0 \times 10^{-5}$ s^{-1}, $k_1^{\mathrm{HO}}K_{\mathrm{w}} = 3.7 \times 10^{-14}$ s^{-1}, $k_2^{\mathrm{H}} = 1.5 \times 10^{-7}/k_1$ M^{-1} s^{-1}, $k_2^{\mathrm{H_2O}} = 1.2 \times 10^{-11}/K_1$ s^{-1}, and $k_{3+5}^{\mathrm{HO}}K_{\mathrm{w}} = 1.1K_2$ s^{-1}, while 3.4×10^{-14} M $< K_1 < 1.1 \times 10^{-11}$ M.

Case D. The remaining possibility requires terms II and III to be the largest term in eq 27 and II > III at low pH; then segment A of the log k_{ly} vs. pH profile represents rate-determining $\mathrm{H_3O^+}$ protonation of **7**; segment B, rate-determining protonation of **7** by $\mathrm{H_2O}$; segment C, rate-determining product formation from **8** catalyzed by water; and segment D, the conversion of **8** to products catalyzed by $\mathrm{HO^-}$. Constants obtained by this analysis are as follows: $K_1 = 3.4 \times 10^{-14}$ M, $k_2^{\mathrm{H}} = 4.3 \times 10^6$ M^{-1} s^{-1}, $k_2^{\mathrm{H_2O}} = 3.4 \times 10^2$ s^{-1}, $k_{3+5}^{\mathrm{H_2O}} = 1.2 \times 10^9K_2$ s^{-1}, and $k_{3+5}^{\mathrm{HO}}K_{\mathrm{w}} = 1.1K_2$ s^{-1}.

In cases B, C, and D, $k_{3+5}^{\mathrm{HO}} = 1.1K_2$ s^{-1}. The reasonableness of this relationship may be assessed by the estimation of K_2 and k_5^{HO} by independent means. From the data of Holmquist and Bruice[13] on base-catalyzed ($\mathrm{B_{AC}2}$) hydrolysis of esters $\mathrm{X{-}CH_2CO_2C_6H_4NO_2}$-*o*, Taft's ρ value was calculated to be 3.63 (eq 29) and from the known σ_{I} values of $-\mathrm{CN}$ and $-\mathrm{CH(OH)C_6H_5}$

$$\log k^{\mathrm{HO}}/k_0^{\mathrm{HO}} = \rho\sigma_{\mathrm{I}}$$

$$\rho = 3.63 \text{ for } \mathrm{XCH_2COOC_6H_4NO_2}\text{-}o^{13} \tag{29}$$

$$\rho = 3.91 \text{ for } \mathrm{XCH_3COOEt}^{17}$$

(0.58 and 0.14, respectively),[14] there may be calculated the value of the second-order rate constant for $\mathrm{B_{AC}2}$ hydrolysis of $\mathrm{C_6H_5CH(OH)CH(CN)CO_2C_6H_4NO_2}$-*o* as 1.2×10^4 M^{-1} s^{-1}. The rate constant for the *o*-nitrophenyl ester may also be calculated in the following manner. From the known rate constant for spontaneous hydrolysis ($k^{\mathrm{H_2O}}$) of $\mathrm{NCCH_2CO_2C_6H_4NO_2}$-*o* and the equation of Holmquist and Bruice[13] (eq 30) relating $k^{\mathrm{H_2O}}$ to the

$$\log k^{\mathrm{HO}} = 0.84 \log k^{\mathrm{H_2O}} + 8.0 \tag{30}$$

rate constant for $\mathrm{B_{AC}2}$ hydrolysis (k^{HO}), the hypothetical rate constants for *o*-nitrophenyl cyanoacetate may be calculated as 7.4×10^3 M^{-1} s^{-1}. This value in conjunction with eq 29 and the σ_{I} for the $-\mathrm{CH(OH)C_6H_5}$ substituent provides the second-order rate constant for alkaline hydrolysis of the *o*-nitrophenyl ester as 2.4×10^4 M^{-1} s^{-1}. The next step of approximating k_5^{HO} relates to the influence of the pK_{a} of the conjugate acid of the leaving group (p$K_{\mathrm{a}}^{\mathrm{LG}}$) upon the rate of alkaline hydrolysis (eq 31). By

$$\log (k^{\mathrm{HO}}/k_0^{\mathrm{HO}}) = \beta(\mathrm{p}K_{\mathrm{a}}^{\mathrm{LG}} - \mathrm{p}K_{\mathrm{a}}{}^{\mathrm{LG}}{}_0)$$

$$\beta = 0.26 \text{ for a series of } \mathrm{CH_3CO_2R}^{15} \tag{31}$$

$$\beta = 0.25 \text{ for a series of } \mathrm{NCCH_2CO_2R}^{16}$$

this method $k_5^{\mathrm{HO}} = \sim 1.3$–$2.5 \times 10^4$ M^{-1} s^{-1}. The third method of approximating k_5^{HO} is as follows: the rate constant for the alkaline hydrolysis of $\mathrm{PhC(OH)HCH(CN)CO_2Et}$ may be estimated from the published rate constants for alkaline hydrolysis of esters $\mathrm{XCH_2CO_2Et}$ (data are taken from the review article of Kirby,[17] eq 29). The change of rate constant upon substitution of $\mathrm{EtO^-}$ leaving group by *p*-nitrophenoxide may then be estimated by use of eq 31, which provides the rate constant (k_5^{HO}) as 9.9×10^4 M^{-1} s^{-1}. The three methods of calculation of k_5^{HO} are in reasonable agreement.

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Table III. Rate Constants for the Acid-Catalyzed and Spontaneous Departure of Hydroxide in E1cB Dehydration

reaction	k_{-1}^{H} (M^{-1} s^{-1})	$k_{-1}^{H_2O}$ (s^{-1})
eq 40[a]	4.0×10^{10}	7.8×10
eq 39[b]	$>4.0 \times 10^{6}$	$>1.4 \times 10^{-1}$
eq 41[c]	1.47×10^{5}	5.5×10^{-1}
eq 42[d]	8×10^{3}	83×10^{-6}

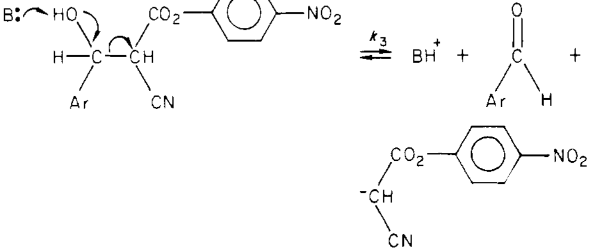
[a] Reference 28. [b] This work; see Table VI of Appendix. [c] Reference 4c. [d] Reference 22.

We have previously shown that the pK_a for carbanion formation from esters $NCCH_2CO_2R$ is related to the pK_a of the conjugate acid of the –OR leaving group (pK_a^{LG}) by eq 32.[16] From this

$$pK_a = 0.36pK_a^{LG} + 5.99 \qquad (32)$$

relationship the pK_a for carbanion formation from $NCCH_2CO_2C_6H_4NO_2$-*p* is 8.57 ± 0.1. From the known dependence of the pK_a of carbon acids $RCH(NO_2)_2$[18] upon the nature of R, one can estimate that the replacement of R = H by R = $C_6H_5CH(OH)$– decreases pK_a by 0.15 unit so that the pK_a of **10** in water is calculated to be 8.42. This value, when corrected for transfer from H_2O to 50% H_2O–CH_3CN (v/v), becomes 9.2.[19] From the product ratio (i.e., $[\mathbf{2}]_\infty/[\mathbf{6}]_\infty$), the rate ratio k_5^{HO}/k_{3+5}^{HO} is calculated to be 0.79. If as predicted by cases B, C, and D, $k_{3+5}^{HO}K_w = 1.1K_2$ s^{-1}, it follows that $k_5^{HO} = 2.2 \times 10^6$ M^{-1} s^{-1} ($K_w = 10^{-15.6}$ in 50% H_2O–CH_3CN).[20] Thus, the value of k_5^{HO} *required* of cases B, C, and D is ~100-fold greater than that *predicted* on the basis of eq 29 or 30 and upon the influence of pK_a^{LG} on carbon acid pK_a (eq 31). For case A, $k_{3+5}^{HO}K_w > 1.1K_2$ s^{-1} so that k_5^{HO} calculated for the $B_{AC}2$ hydrolysis of **8** would exceed 2.2×10^6 M^{-1} s^{-1} and, therefore, exceed the anticipated rate constant by >100-fold. It should be pointed out that the hypothetical rate constant for $B_{AC}2$ hydrolysis of $NCCH_2CO_2C_6H_4NO_2$-*o* (calculated from eq 30) is 100-fold less than the observed rate constant for E1cB hydrolysis.[1b,16] These considerations strongly disfavor Scheme IV in favor of the ketene mechanism implied in Scheme III.

Another argument against the mechanisms of Scheme IV comes from the rate ratio, $k_3^{HO}/k_3^{H_2O}$, which is calculated to be 3×10^4 on the basis of the product ratio. Since these rates reflect the hydroxide- and water-catalyzed breakdown of **8** into **6** and the conjugate base of *p*-nitrophenyl cyanoacetate, the Brønsted β value may be calculated as 0.3 from the rate ratio. Since the k_3 process is the reverse reaction of the addition of a carbanion upon anisaldehyde, the calculated Brønsted β value is unreasonably small, because the addition of a strong base such as a carbanion requires little or no general acid catalysis[21] (α is quite small), which means that the reverse reaction (k_3 process) borders between general base and specific base catalysis (β is large or 1.0).



(33)

Combination of the reaction sequences of Schemes II, III, and IV together with the reaction sequence of the retro-Knoevenagel condensation of **3** gives Scheme V. The correct pathway for ester hydrolysis is, as shown, via the ketene mechanism to provide **9**. As noted (Results) compound **2** accumulates in the course of hydrolysis of **1**; the reaction sequence **2** → **9** → **10** → **6** has been studied. No intermediate can be observed spectrophotometrically between **2** and **6**. The steady-state assumption in **9** and **10** provides eq 34. Three situations may prevail. If hydroxide attack upon **2** is rate determining, then eq 34 provides eq 35. On the other hand, if the rate-limiting step is protonation of **9**, then eq 36 is obtained, and if C–C bond scission is rate limiting, then eq 37 pertains ($K_2 = k_{-2}^{H_2O}/k_2^{H} = k_{-2}^{HO}K_w/k_2^{H_2O}$). It is experimentally observed that the rate of hydrolysis of **2** is first order in [HO⁻], a feature of eq 35, 36, and 37.

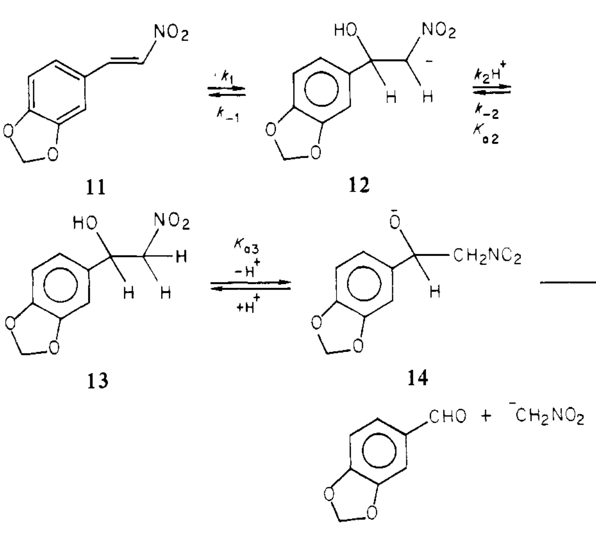
$$k_{obsd} = \{\sum k_1[\text{base}]\sum k_2[\text{acid}]\sum k_3[\text{base}]\}/\{\sum k_2[\text{acid}]\sum k_3[\text{base}] + \sum k_3[\text{base}]\sum k_{-1}[\text{acid}] + \sum k_{-1}[\text{acid}]\sum k_{-2}[\text{base}]\} \qquad (34)$$

$$k_{obsd} = \sum k_1[\text{base}] = k_1^{HO}[HO^-] \qquad (35)$$

$$k_{obs} = \frac{k_1\sum k_2[\text{acid}]}{k_{-1}a_H} = \frac{K_1k_2^{H_2O}}{a_H} \qquad (36)$$

$$k_{obsd} = \frac{K_1}{K_2}\sum k_3[\text{base}] = \frac{K_1}{K_2}k_3^{HO}[HO^-] \qquad (37)$$

Crowell and Kim, in their study of the retro-Knoevenagel condensation of 3,4-methylenedioxy-β-nitrostyrene (eq 38), reported the constants to be $K_{a2} = 1.7 \times 10^{-9}$, $K_{a3} = 1 \times 10^{-14}$ (an estimated value), $k_{-2}^{HO} = 2.9 \times 10^{-2}$ M^{-1} s^{-1}, and $k_3^{HO} = 2 \times 10^3$ M^{-1} s^{-1} (k_3^{HO} representing the overall rate constant for the conversion of **13** to the products).[22] From these data one can discern that despite the fact that the pK_a of the hydroxyl group is much larger than the pK_a of the carbon acid, the ionization of the alcohol and C–C bond scission (k_3 process) is kinetically a more facile process than is the ionization of the carbon acids (k_{-2}). In the instance of **10**, the proton on the carbon atom is much more weakly acidic than is the proton on the hydroxyl group (vide infra) and ionization of the O–H bond with accompanying C–C bond scission (k_3 process) should proceed much more rapidly than ionization of the C–H bond. Thus, C–C bond scission cannot be the rate-determining step, and the operation of eq 37 is ruled out. The large negative activation entropy for retro-Knoevenagel condensation of **2** also supports this argument. This finding provides additional evidence against the mechanisms of Scheme IV accounting for the hydrolysis of **1**. If the carbon acid **8** were to be hydrolyzed by means of the $B_{AC}2$ mechanism, **10** would be formed and since C–C bond scission proceeds much more rapidly than the formation of **2** from **10**, **2** could not accumulate as an



(38)

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(18) Tselenskii, I. V.; Kosmynina, A. S.; Dronov, V. N.; Shokhor, I. N. *Reaktsion Sposobnoet' Org. Soedin* **1970**, 50; quoted in J. R. Jones "The Ionization of Carbon Acids", Academic Press: New York, 1973; p 70; and Reutov, O. A.; Beletskaya, I. P.; Butin, K. P. "CH-Acids"; Pergamon Press: New York, 1978; p 62.

(19) Solvent effects were estimated by the difference of pK_a values of phenols and $NCCH_2COSC_6H_5$ in water and in 50% aqueous acetonitrile.

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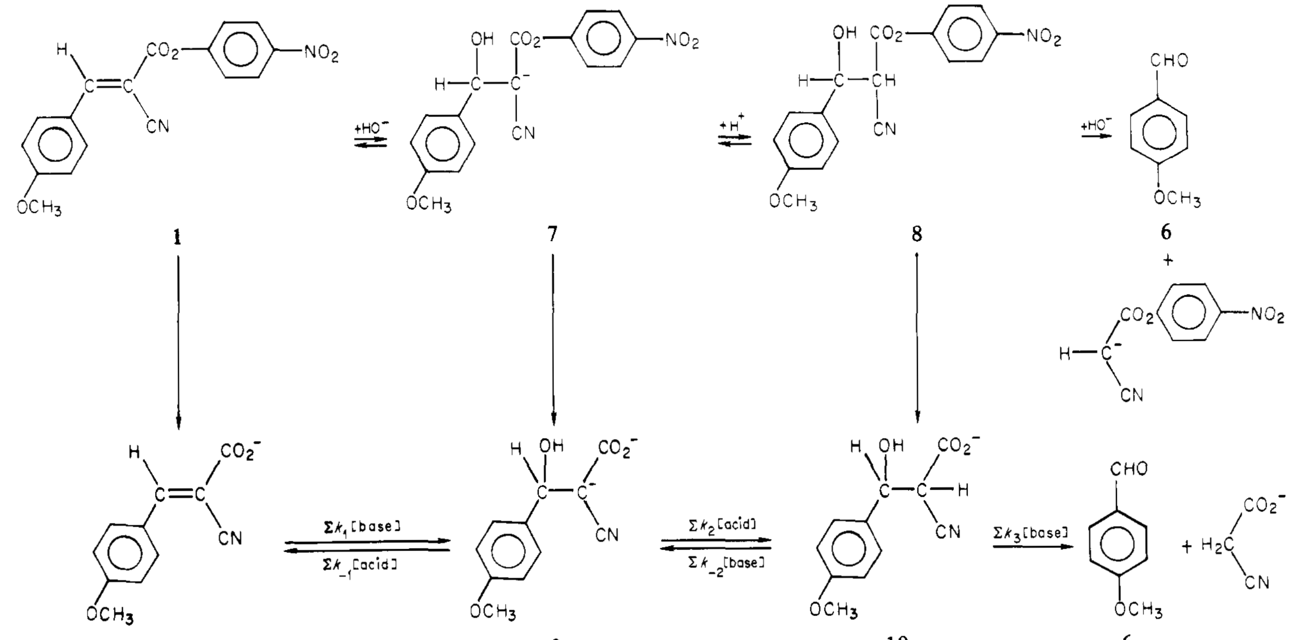
Scheme V



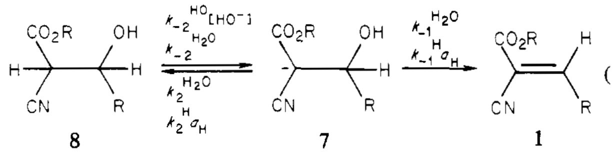
1 7 8 6

2 9 10 6

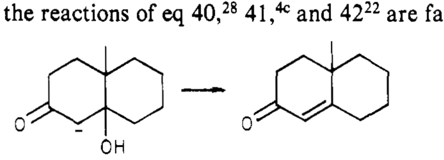
intermediate. However, **2** was seen to accumulate in the hydrolysis of **1**.

Estimations of the pK_a values for carbon acid and hydroxyl group in **10** were made as follows. In a study of the E1cB mechanism for hydrolysis of nitrophenyl hydrogen malonates, Kirby and Lloyd[23] concluded that the dianion $ArOCOCH(-)CO_2^-$ was much more stable than predicted on the basis of the σ_I value ($\sigma_I = 0.85$) of the $-CO_2^-$ group. They suggested the use of the σ_p^- substituent constant in estimating the pK_a of carbon acids ($>$CH–X; σ_p^- value of CO_2^- group was reported to be 0.24). Employing this suggestion, the pK_a of $NC-CH_2-CO_2^-$ has been estimated from a series of cyanocarbon acids to be $pK_a \simeq 20-21$. In a separate experiment $C_6H_5CH_2CH(CN)CO_2^-$ was spectrophotometrically titrated, but the formation of carbanion could not be detected to pH 14, suggesting that the pK_a for the formation of dianion is much greater than 14. The pK_a of the hydroxyl function of **10** was estimated from the relationship $pK_a = 15.6 - 6.97\sigma_I$ ($r = 0.96$, $n = 8$ for substituted methanols)[25] as $pK_a \simeq 14$. Thus, for **10** the proton on oxygen is believed to be much more acidic than the proton on carbon.

The conversion of **8** to **1** (eq 39) represents dehydration via a carbanion intermediate. Such reactions have not been thoroughly studied, are common in biochemistry and are, therefore, of interest.[26] At high pH the $(\mathrm{E1cB})_{\mathrm{anion}}$ mechanism is operating where **7** is more stable than **8** and C–O bond cleavage is rate determining, while at low pH, formation of carbanion is rate limiting with rapid cleavage of the C–O bond ($(\mathrm{E1cB})_\mathrm{I}$ mechanism) because $k_2^{H_2O} + k_2^{H}a_H << k_{-1}^{H_2O} + k_{-1}^{H}a_H$ (irreversible formation of the carbanion). The finding that the departure of HO^- from carbanion is acid catalyzed deserves comment. In competition between the stepwise E1cB mechanism and the concerted E2 elimination, the latter is generally considered to prevail when a strongly basic leaving group is involved.[27] Apparently the stepwise mechanism also prevails when the departure of poor (strongly basic) leaving groups is assited by acid catalysis. The catalysis for departure of the hydroxyl leaving group is most likely general in nature, since H_2O is a very good leaving group. The rate constants for acid catalysis of the reactions of eq 40,[28] 41,[4c] and 42[22] are favorably comparable to k_{-1}^{H} of eq 39 (Table III). It must be noted that the magnitude of the rate constant increases as the negative charge localizes on the carbon atom β to the leaving hydroxide group.



8 7 1 (39)



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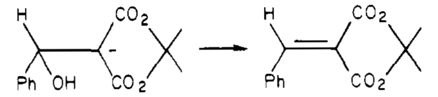

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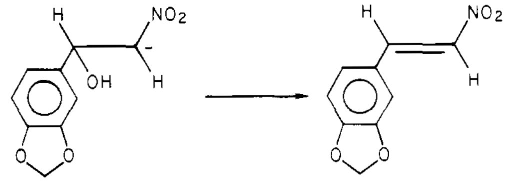

12 11 (42)

The departure of p-nitrophenoxide and HO^- from **7** amounts to the E1cB elimination of a weakly basic (good) leaving group and a strongly basic (poor) leaving group from **8** (eq 43). Surprisingly, these two parallel reactions are competitive in the absence of buffer catalysis. This may be ascribed to (i) the greater free-energy content of the ketene product and (ii) the cleavage of p-nitrophenoxide requiring the ester carbanion to be in energetically unfavorable conformation (**15**) wherein the delocalization energy of the enolate anion system is lost.[16] For this reason, E1cB eliminations are effective with much poorer leaving groups than are E1cB ester hydrolyses.

The ketene mechanism of ester hydrolysis is usually refered to as the "E1cB mechanism" or the "elimination–addition mechanism". This terminology is not correct in the present case

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(25) Data are taken from the review article of C. H. Rochester, ref 5b, p 327.

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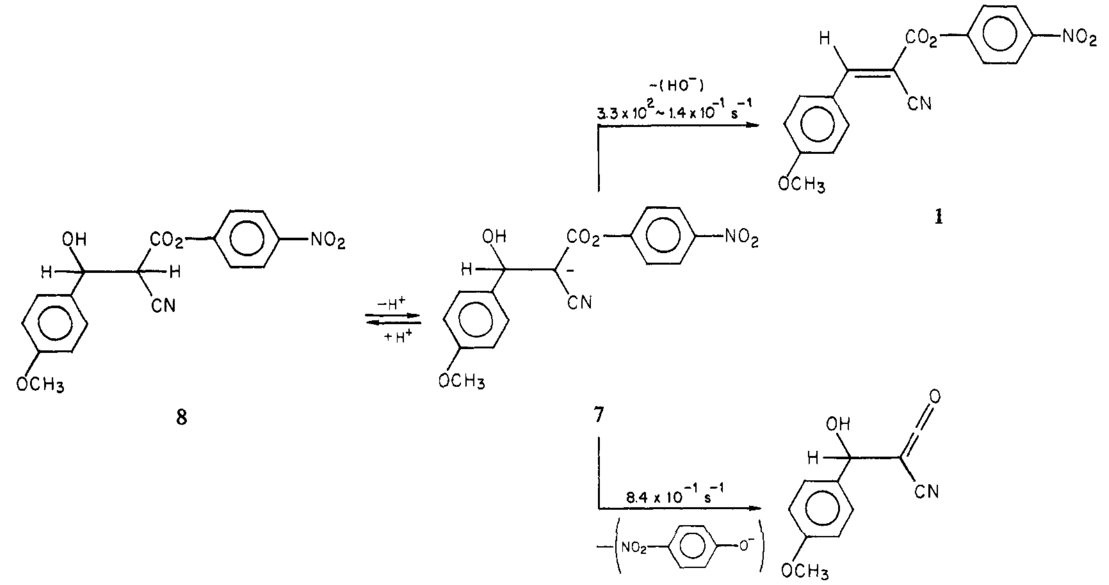
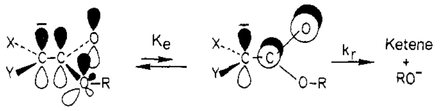


(43)

Table IV. Mechanistic Classification of Allylic Substitution Nu: + $=\!\!\diagdown$— L

	description	kinetic order	symbol	related elimination
	first-order carbanion	1st	$(\mathrm{SN1'C^-})_{\mathrm{anion}}$	$(\mathrm{E1cB})_{\mathrm{anion}}$
extent of Nu–C bond order	preequilibrium carbanion	2nd	$(\mathrm{SN1'C^-})_{\mathrm{R}}$	$(\mathrm{E1cB})_{\mathrm{R}}$
	second-order anion	2nd	$(\mathrm{SN1'C^-})_{\mathrm{I}}$	$(\mathrm{E1cB})_{\mathrm{I}}$
	concerted	2nd	SN2′	E2
extent of C–L bond order	cation	1st	SN1′	E1



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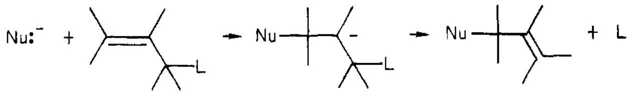
(44)

because the overall reaction from **1** to the ketene is not an elimination reaction, but an allylic substitution reaction (eq 46). Many papers have dealt with allylic substitutions, but suggestions of the operation of this carbanion mechanism are rare.[29] Proper terminology would be allylic substitution via carbanion, unimolecular reaction in the carbanion and may be symbolized as "SN1′C⁻". As the E1cB mechanism is subclassified into three classes, this mechanism can also be subclassified into three mechanisms.[26b]



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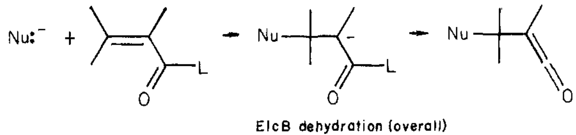

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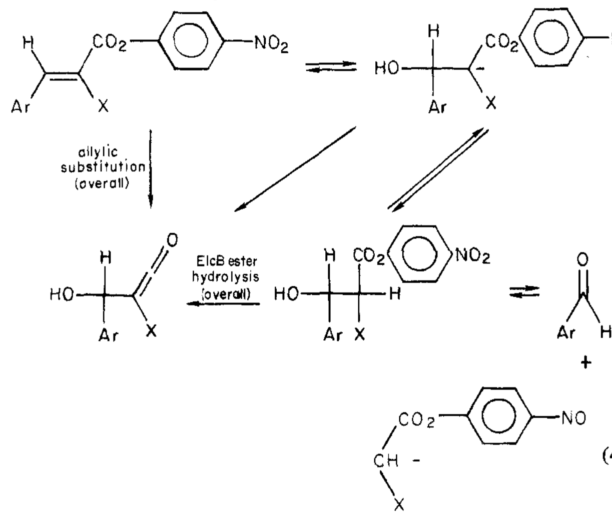
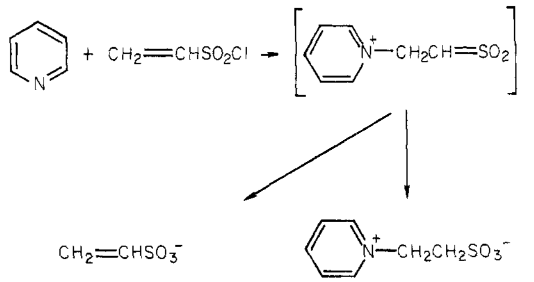


(47)

The overall reaction from **2** to **2** (**1** → **7** → the ketene intermediate → **9** → **2**) reminds us of the "vinylogous nucleophilic catalysis" proposed by King et al.[30] They showed the hydrolysis of ethenesulfonyl chloride in the presence of pyridine takes place by the reaction sequence in eq 48. We believe that this reaction also proceeds by the stepwise mechanism as is shown in this paper (i.e., nucleophilic attack of pyridine on the double bond to yield a carbanion (betaine) followed by the departure of the leaving group (chloride)).



(48)

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

Registry No. 1, 80540-67-6; **2**, 1519-55-7; **3**, 80540-68-7; **4**, 1011-92-3; **5**, 69727-07-7; **6**, 123-11-5; *p*-nitrophenol, 100-02-7.

Supplementary Material Available: Appendix (simplification of eq 11), Table V (six sets of conditions), and Table VI (rate constants for hydrolysis of **1**) (11 pages). Ordering information is given on any current masthead page.

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