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Mechanistic Change from $(\mathrm{ElcB})_R$ to $(\mathrm{ElcB})_i$ Brought about by a Sterically Bulky Substituent in Ester Hydrolysis

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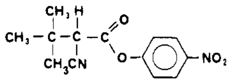
The anticipated pH dependence of log k_{rate} for ElcB ester hydrolysis reactions is discussed. Rate constants for carbon acid ionization and reprotonation with a series of α-cyano esters have been determined over a limited pH range. The pH dependence of the rates of hydrolysis of the esters has also been determined. The $\mathrm{p}K_a{}^{\mathrm{CH}}$ values for C–H bond ionizations provided by the log k_{obsd} vs. pH profiles for the hydrolytic reactions are compared with the $\mathrm{p}K_a$ values for C–H bond ionization determined directly. The dependence of mechanism [$(\mathrm{ElcB})_i$, $(\mathrm{ElcB})_R$, $(\mathrm{ElcB})_{\mathrm{anion}}$] upon steric crowding in the acyl moiety and upon pH is established. Previous conclusions concerning ElcB hydrolysis of aryl phenylmethanesulfonates are discussed.

The ElcB elimination can be subclassified into four mechanisms: (a) $(\mathrm{ElcB})_i$, where rate-determining carbanion formation is followed by departure of the leaving group; (b) $(\mathrm{ElcB})_R$, where the rate constants for interconversion of carbon acid and carbanion are rapid (preequilibrium) and the following departure of the leaving group is rate determining; (c) $(\mathrm{ElcB})_{\mathrm{anion}}$, where carbanion is the ground state; and (d) $(\mathrm{ElcB})_{\mathrm{ip}}$, where a preequilibrium ion pair (or tightly solvated *anion*)[1] is involved. Mechanistic change from $(\mathrm{ElcB})_R$ to $(\mathrm{ElcB})_i$ is usually attributed to an increase in leaving group ability.[1,2]

In a previous paper we discussed our finding that α-*tert*-butylation of a series of esters of cyanoacetic acid resulted in an increase in the pH-independent rates (at alkaline pH) for ester hydrolyses by both ElcB and $\mathrm{B_{Ac}2}$ mechanisms.[3] In this paper we present recent results which pertain to the effect of steric crowding in the acyl moiety on the ElcB mechanism of ester hydrolysis. Among the results is the finding that α-*tert*-butylated *p*-nitrophenyl cyanoacetate (*p*-nitrophenyl 2-cyano-3,3-dimethylbutanoate, 1) is hydrolyzed by means of an $(\mathrm{ElcB})_i$ mechanism at the pH region near the $\mathrm{p}K_a$ of 1, while the parent compound *p*-nitrophenyl cyanoacetate (2) is hydrolyzed by means of an $(\mathrm{ElcB})_R$ mechanism in the same pH region.



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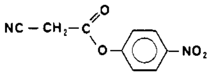

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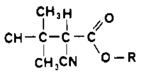

3, 4, 5, 6, 7
R = Et–, CF_3CH_2–, Ph–, *m*-ClC_6H_4–, *m*-NO_2–C_6H_4–

Experimental Section

Materials. Reagent-grade KCl, K_2CO_3, and KH_2PO_4 were used without purification. Commercially available standard solutions of 1 M KOH (carbonate free) and 1 M HCl were used. Acetonitrile was spectral quality. Aqueous solutions were prepared from deionized and freshly double distilled water. Preparation of the esters were reported in the previous paper.[3]

Kinetic measurements were carried out in aqueous acetonitrile (1.0% v/v) at $\mu = 1.0$ (with KCl) and at 30.0 ± 0.1 °C. Full details of kinetic measurements have been provided in the previous paper.[4] The values of pseudo-first-order rate constants were calculated by using a least-squares analysis in determining the slope of the plot of log $[(\mathrm{OD_{inf}} - \mathrm{OD_0})/(\mathrm{OD_{inf}} - \mathrm{OD}t)]$ vs. time. Parameters for the empirical equation were determined by minimizing the summation of squared deviations of the logarithm of the observed rate constant from the logarithm of the value for rate constant calculated by the empirical equation at given pH values.

Results and Discussion

The pH–log rate profile for the hydrolysis of 1 is given in Figure 1. As can be seen in Figure 1, the $[\mathrm{HO^-}]$-dependent rate at the higher pH region is some 20% lower

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[1] Bordwell, F. G. *Acc. Chem. Res.* **1970**, *3*, 281; **1972**, *5*, 374. Bordwell, F. G.; Westling, M. M.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5950. Saunders, W. H.; Cockerill, A. F. "Mechanism of Elimination Reactions"; Wiley: New York, 1973.

[2] For the review articles on ElcB or "elimination–addition" mechanism in ester hydrolysis: William, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627. Douglas, K. T. In "Progress in Bioorganic Chemistry"; Kaiser, E. T., Kezdy, E. J., Eds.; Wiley: New York, 1976; Vol. 4.

[3] Inoue, M.; Bruice, T. C. *J. Org. Chem.* **1983**, *48*, 3559.

[4] Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 3003.

0022-3263/86/1951-0959$01.50/0

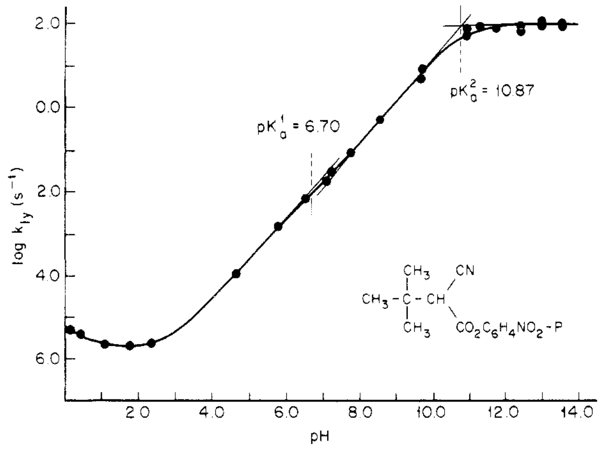
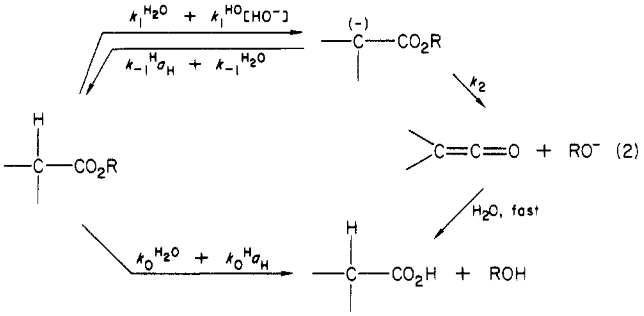


Figure 1. pH vs. log (k_{1y}, s^{-1}) profiles for hydrolysis of *p*-nitrophenyl 2-cyano-3,3-dimethylbutanoate (**1**).

than the [HO$^-$]-dependent rate at the lower pH region. The pH–rate profile for the ester can be fit by using the empirical eq 1 where $K_E{}^1$ and $K_E{}^2$ are two kinetically apparent acid dissociation constants. The computer-optimized parameters used to fit eq 1 to the points of Figure 1 are as follows: $k_E{}^1$, 5.2×10^{-6} M^{-1} s^{-1}; $k_E{}^2$, 1.86×10^{-6} s^{-1}; $K_E{}^1k_E{}^3$, 1.40×10^{-9} M s^{-1}; $K_E{}^1$, 1.98×10^{-7} M; $K_E{}^2k_E{}^4$, 1.05×10^{-9} M s^{-1}; and $K_E{}^2$, 1.46×10^{-11} M. A pH–log rate profile exhibiting inflections indicative of two apparent pK_a's was observed in the hydrolysis of nitrophenyl acetoacetates[5,6] and was fully analyzed by Pratt and Bruice on the basis of eq 1 for the reaction scheme of eq 2.[6]

$$k_{1y} = k_E{}^1 a_H + k_E{}^2 + \frac{K_E{}^1 k_E{}^3}{K_E{}^1 + a_H} + \frac{K_E{}^2 k_E{}^4}{K_E{}^2 + a_H} \tag{1}$$



However, the logic for derivation of rate constants based on the above reaction scheme cannot be applied to the present case, because the empirical values of $K_E{}^1k_E{}^3$ and $K_E{}^2k_E{}^4$ are very close to each other, and since the fourth term of the empirical equation cannot be neglected even at low pH.

By applying the "improved steady-state assumption"[7] to the carbanion, the pseudo-first-order rate constants (k_{1y}) may be expressed by eq 3. As $k_{-1}{}^H = k_1{}^{H_2O}/K_a{}^{CH}$ and

$$k_{1y} = k_0{}^H a_H + k_0{}^{H_2O} + \frac{(k_1{}^{HO}[HO^-] + k_1{}^{H_2O})k_2}{(k_1{}^{HO}[HO^-] + k_1{}^{H_2O}) + (k_{-1}{}^{H_2O} + k_{-1}{}^H a_H) + k_2} \tag{3}$$

$k_{-1}{}^{H_2O} = k_1{}^{HO}K_w/K_a{}^{CH}$, the above theoretical equation can be transformed into eq 4. Multiplying both denominator and numerator of the third term of eq 4 by $(K_a{}^{CH}a_H/k_1{}^{H_2O})$ yields eq 4a. On the other hand, the empirical equatio (eq 1) can be transformed into the following equation:

$$k_{1y} = k_0{}^H a_H + k_0{}^{H_2O} + \left\{ \frac{\left(\frac{K_1{}^{HO}K_w}{a_H} + k_1{}^{H_2O} \right) k_2}{\frac{k_1{}^{HO}K_w}{\mathrm{a}_H} + k_1{}^{H_2O} + \frac{k_1{}^{HO}K_w}{K_a{}^{CH}} + k_2 + \frac{k_1{}^{H_2O}a_H}{K_a{}^{CH}}} \right\} \tag{4}$$

$$k_{1y} = k_0{}^H a_H + k_0{}^{H_2O} + \frac{\frac{K_a{}^{CH}K_w k_1{}^{HO} k_2}{k_1{}^{H_2O}} + \mathrm{K_a{}^{CH}k_2a_H}}{\frac{K_a{}^{CH}k_1{}^{HO}K_w}{k_1{}^{H_2O}} + \left\{ K_1{}^{H_2O} + \frac{k_1{}^{HO}K_w}{K_a{}^{CH}} + k_2 \right\} \frac{K_a{}^{CH}a_H}{k_1{}^{H_2O}} + (a_H)^2} \tag{4a}$$

$$k_{1y} = k_E{}^1 a_H + k_E{}^2 + \frac{(k_E{}^3 + k_E{}^4)K_E{}^1K_E{}^2 + (k_E{}^3K_E{}^1 + k_E{}^2K_E{}^4)a_H}{K_E{}^1K_E{}^2 + (K_E{}^1 + K_E{}^2)a_H + a_H{}^2} \tag{5}$$

This equation is of the same form as the theoretical equation (eq 4a) so that direct comparison of the two equations gives $k_0{}^H = k_E{}^1$ and $k_0{}^{H_2O} = k_E{}^2$ as well as the following four equations:

$$(K_a{}^{CH}K_w k_1{}^{HO}k_2)/k_1{}^{H_2O} = (k_E{}^3 + k_E{}^4)\, K_E{}^1K_E{}^2 = 2.08 \times 10^{-16}\ \mathrm{M^2\ s^{-1}} \tag{6}$$

$$K_a{}^{CH}k_2 = k_E{}^3K_E{}^1 + k_E{}^2K_E{}^4 = 2.45 \times 10^{-9}\ \mathrm{M\ s^{-1}} \tag{7}$$

$$(K_a{}^{CH}k_1{}^{HO}K_w)/k_1{}^{H_2O} = K_E{}^1K_E{}^2 + 2.88 \times 10^{-18}\ \mathrm{M^2} \tag{8}$$

$$(k_1{}^{H_2O} + k_1{}^{HO}K_w/K_a{}^{CH} + k_2)(K_a{}^{CH}/k_1{}^{H_2O}) = K_E{}^1 + K_E{}^2 = 1.98 \times 10^{-7}\ \mathrm{M} \tag{9}$$

From these four equations, all the rate constants can be determined as[8,9] $\mathrm{K}_1{}^{H_2O} = 2.18 \times 10^{-2}$ s^{-1}, $k_{-1}{}^H = 6.40 \times 10^8$ M^{-1} s^{-1}, $k_1{}^{HO} = 1.27 \times 10^{-5}$ M^{-1} s^{-1}, $k_{-1}{}^{H_2O} = 5.43 \times 10$ s^{-1}, $K_a{}^{CH} = 3.40 \times 10^{-11}$ M (p$K_a{}^{CH}$ = 10.45), $k_2 = 7.21 \times 10$ s^{-1}.

Before continuing further with the discussion of the present results, we consider the interpretation of the two types of pH–rate profiles which can, in principal, be generated from the reaction scheme of eq 2. Figure 2A shows a pH–log rate profile with an apparent pK_a. In the figure observable hydrolysis rates are given by the bold line and the component profiles for each term of eq 2 are provided by fine lines. Segment A is generated by the first term ($k_0{}^H a_H$) of the theoretical equation and in this region hydrolysis is an acid-catalyzed reaction. Segment B is expressed by the second term of the theoretical equation ($k_0{}^{H_2O}$) and in this region hydrolysis proceeds spontaneously and is generally accepted to be caused by water-catalysed nucleophilic attack of water. Segment C is expressed by $k_{obsd} = k_2K_a{}^{CH}[HO^-]/K_w$, and in this region the carbanion is in equilibrium with carbon acid and spontaneously breaks down into ketene and alkoxide. Segment D is expressd by $k_{obsd} = k_2$, and in this region carbanion becomes a stable ground state. As is illustrated in Figure 2A, the line providing $k_{-1}{}^{H_2O}$ always exists above segment D (in other words, spontaneous protonation of the carbanion proceeds much faster than breakdown of the carbanion into ketene and alkoxide), and the line providing $k_1{}^{HO}[HO^-]$ always resides above segment C. It must be noted that in this situation the kinetically apparent pK_a is that of the true p$K_a{}^{CH}$.

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(5) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993.

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

(7) McDaniel, D. H.; Smoot, C. R. *J. Phys. Chem.* **1959**, *60*, 966.

(8) Calculated on the basis of pK_w = 13.833: Robinson, R. A.; Stokes, R. H. "Electrolyte Solutions"; Butterworths: London, 1959; p 544.

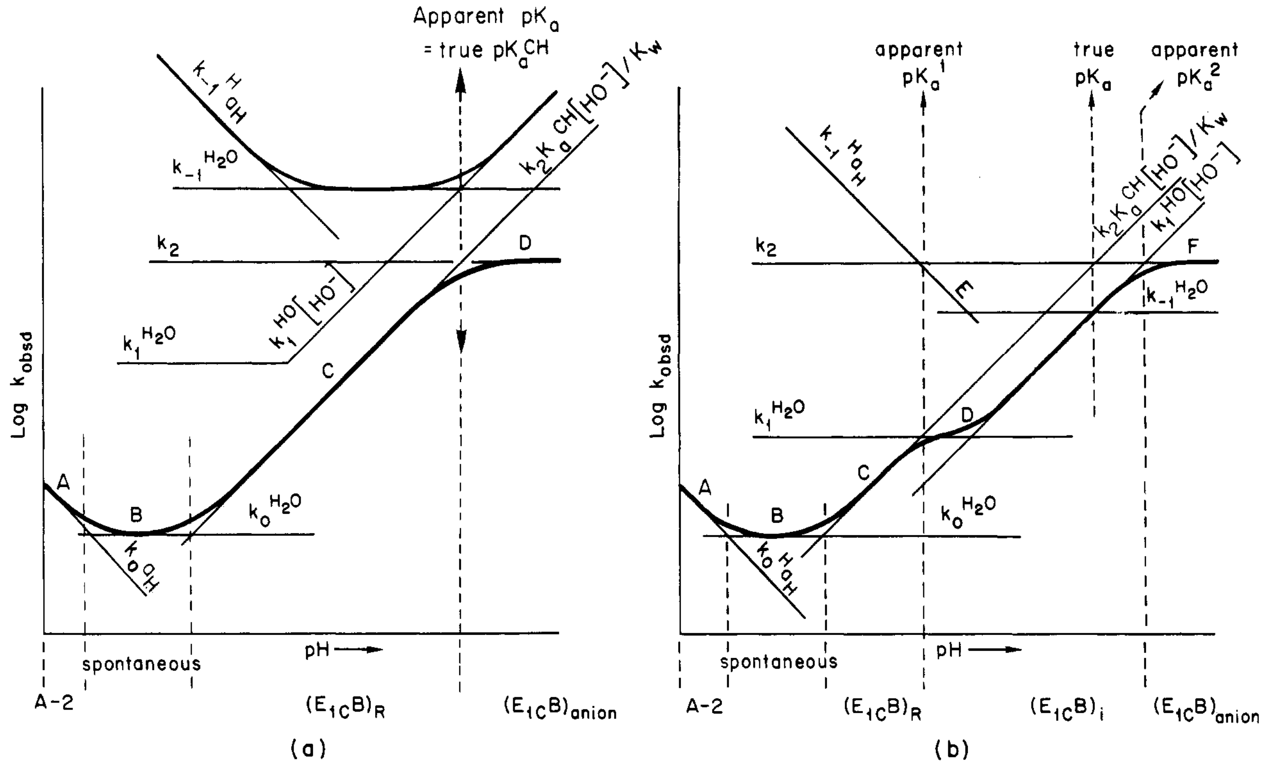

Figure 2. Outlined pH–rate profileds for ElcB ester hydrolysis to illustrate the correlation between observed rate and rate for elementary processes: (A) pH rate profile with an apparent pK_a; (B) pH rate profile with two apparent pK_a's.

Profound changes are made in the log rates vs. pH profile by changes in the partition coefficient ($k_2/k_{-1}^{H_2O}$) for the carbanion by increase in k_2 or decrease in $k_{-1}^{H_2O}$ brought about by structural alteration of the carbon acid. As long as $k_{-1}^{H_2O}$ is larger than k_2, the pH–rate profile with one apparent pK_a will be held. Then, when $k_{-1}^{H_2O}$ becomes smaller than k_2, as in the case of hydrolysis of nitrophenyl acetoacetates, the rate of carbanion formation (i.e., $k_1^{HO}[HO^-]$) becomes slower than the hypothetical hydrolysis rate for preequilibrium formation of carbanion followed by the breakdown of the carbanion (i.e., $k_2K_a^{CH}[HO^-]/K_w$, viz. segment C). Under these conditions the pH–log rate profile with one apparent pK_a gives way to one with two apparent pK_a's as shown in Figure 2B. In Figure 2B the chemical meanings of segment A, B, and C are the same as those in Figure 2A (loc. cit.). By a comparison of lines providing the profiles for the individual terms of eq 2 (i.e., k_2, $k_1^{HO}[HO^-]$, $k_1^{H_2O}$, $k_{-1}^{H_2O}$, and $k_{-1}^{H}a_H$), it is seen that k_2 is the largest among the five rate terms at the pH region near pK_a^{CH}. Since the four smaller terms may be neglected,[10] the third term of the theoretical equation (eq 3) will become $k_1^{H_2O} + k_1^{HO}[HO^-]$. Thus, segment D in Figure 2B is expressed by rate-determining proton transfer from the ester to water ($k_1^{H_2O}$) followed by rapid breakdown of the resulting carbanion. Similarly, segment E is expressed by rate-determining proton transfer from the ester to hydroxide ($k_1^{HO}[OH^-]$) followed by rapid breakdown of the carbanion into ketene and alkoxide. In the pH region corresponding to segment D and E (i.e., between the two apprent pK_a's), breakdown of the carbanion into ketene and alkoxide proceeds much faster than the formation of carbanion from the ester, so that hydrolysis follows an $(E1cB)_i$ mechanism in this pH region. For this situation, neither of the apparent pK_a's agree with the true pK_a values.[11]

Returning to the discussion of the hydrolysis of 1, it may be recalled that a dicarbanion was proposed as an intermediate in the hydrolysis of aryl (methylsulfonyl)methanesulfonate (i.e., $MeSO_2C^{2-}SO_3A_r$).[12] If both monoanion and dianion are formed and these anionic species yields product via elimination, then the pH–rate profile would resemble that of Figure 2B, where the lower pK_a^1 corresponds to the first ionization and the higher pK_a^2 corresponds to the second ionization. Such a situation cannot prevail in the hydrolysis of 1, since formation of a dicarbanion is not possible. The observation of two apparent pK_a values in the kinetics for hydrolysis of 1 suggests to us that proton transfer from 1 is slow when compared with that of 2.[13] To substantiate this expec-

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(9) Because k_{1y} was determined by extrapolation of observed rate constants to zero buffer concentration, the calculated rate constants for $k_1^{H_2O}$ and k_{-1}^{H} are of little significance. For detailed discussion, see ref 6.

(10) In the hydrolysis of nitrophenylacetoacetates, as studied by Pratt and Bruice, k_2 was sufficiently greater than the other four rates that they could be ignored. In the hydrolysis of 1, however, k_2 (7.21 × 10 s^{-1}) is almost comparable to $k_{-1}^{H_2O}$ (5.43 × 10 s^{-1}) so that the latter cannot be neglected. It is for this reason that we have had used a rather more complicated kinetic derivation than used by Pratt and Bruice.

(11) Detailed inspection of Figure 2A,B reveals that there can be another possible pH–rate profile derived from the reaction scheme shown in eq 2. Figure 2B is derived under the condition that $k_2 > k_{-1}^{H_2O}$ and Figure 2A is derived under the condition that $k_{-1}^{H_2O} > k_2 > k_0^{H_2O}$ (eq 3.), while in additional pH–rate profile is generated if one assumes that $k_0^{H_2O} > k_2$. However, the profile (not shown) rises in going from alkaline to acid pH. A plateau at high pH (k_2) ascends ($k_0^{H_2O}a_H/K_a^{CH}$) to a second plateau ($k_0^{H_2O}$). In going to still lower pH the rate increases ($k_0^{H}a_H$). Such a pH–rate profile has yet to be established in an ElcB ester hydrolysis.

(12) Thea, S.; Guanti, G.; Williams, A. J. Chem. Soc., Chem. Commun. 1981, 535.

(13) Th ElcB mechanism shown in the scheme depicted in eq 2 is not the sole mechanism capable of displaying two apparent pK_a's in a plot of log k_{1y} vs. pH; However, it is the simplest. Two apparent kinetic pK_a's could arise from a $B_{AC}2$ like mechanism, if the carbanion were off the reaction path and products arose from both anionic and dianionic tetrahedral intermediates. Such a mechanism is most unlikely for the hydrolysis of a p-nitrophenyl ester. Also, it could not apply to the hydrolysis of 1. Analysis of the kinetic data for 1 in terms of such a mechanism shows that for it to allow a fit of Figure 1 there would be required a rate constant of 10^{13} s^{-1} for the protonation of dianionic tetrahedral intermediate or unacceptably low pK_a values for anionic species. In addition a $B_{AC}2$ mechanism of this sort cannot explain the large negative β_{lg} values reported in the previous paper.[3]

Table I. Rates of Carbanion Formation

ester	pH	λ, nm	k_{obsd}^{ioniz}, s^{-1}	pK_a^{CH}	k_1^{HO},[a] $M^{-1} s^{-1}$	$k_{-1}^{H_2O}$,[b] s^{-1}
3	13.35	260	$\approx 6.2 \times 10^2$	≈ 14.5[c]	$\approx 1.2 \times 10^{-1}$	$\approx 5.6 \times 10^{-2}$
4	12.41	265	$\approx 7.8 \times 10^2$	11.95	$\approx 1.5 \times 10^4$	$\approx 2.0 \times 10^2$
5	10.88	243	4.42×10^2	11.94	3.21×10^4	4.07×10^2
	11.72	260	5.96×10^2		2.93×10^4	3.71×10^2
	12.41	265	$\geq 1.2 \times 10^3$		$\geq 2.4 \times 10^4$	$\geq 3.0 \times 10^2$
6	10.88	260	2.52×10^2	11.53	4.12×10^4	2.06×10^2
	10.88	250	2.51×10^2		4.10×10^4	2.05×10^2
	11.72	260	5.74×10^2		4.54×10^4	2.27×10^2
	12.41	260	$\geq 7.2 \times 10^{-2}$		$\geq 1.7 \times 10^4$	$\geq 0.84 \times 10^2$
7	10.88	255	2.23×10^2	11.05	8.06×10^4	1.33×10^2

[a] Calculated rate constants for hydroxide-catalyzed deprotonation from the carbon acids; $k_1^{HO} = K_a^{CH} a_H k_{obsd}^{ioniz}/(a_H + K_a^{CH})K_w$. [b] Calculated rate constants for spontaneous protonation for the carbanion; $k_{-1}^{H_2O} = k_{obsd}^{ioniz} a_H/(K_a^{CH} + a_H)$. [c] Estimated from slight curvature of profile of pH vs. log rate plot determined up to pH 13.8 and from correlation between pK_a^{CH} values of a series of cyanoacetates and those of 2-cyano-3,3-dimethylbutanoates.

tation, the proton-transfer rate for a series of esters (**3** to **7**) with leaving groups whose ability is less than *p*-nitrophenoxide were explored.

The rate of ionization of the esters was measured directly by use of a stopped-flow spectrophotometer. However, since at low pH the equilibrium lies far to the carbon acid side, the change in optical density on going from carbon acid to the equilibrium state of carbon acid and carbanion was too small to obtain significant results. At high pH values base-catalyzed deprotonation of the carbon acid was at completion within the relaxation period of mixing on the stopped-flow apparatus. For these reasons rate constants could be determined only over a limited pH range. Within this pH range and with esters possessing poorer leaving groups, carbon acid ionization is well-separated in time from the hydrolytic reaction and obeyed the first-order rate law to 90% of completion of reaction. The results are summarized in Table I. Every datum in Table I is the average value of several runs on the stopped-flow apparatus under identical conditions.

The pseudo-first-order rate constants (k_{obsd}^{ioniz}) for attainment of equilibrium in carbon acid and carbanion are equal to the summation of forward (deprotonation) and reverse (protonation) rate constants:

$$k_{obsd}^{ioniz} = k_1^{HO}[HO^-] + k_{-1}^{H_2O} \qquad (10)$$

As $k_{-1}^{H_2O} = k_1^{HO}K_w/K_a^{CH}$ $k_1^{HO}k_w/K_a^{CH}$ eq 10 can be transformed to eq 11. The determined k_{obsd}^{ioniz} were an-

$$k_{obsd}^{ioniz} = k_1^{HO}K_w\left(\frac{1}{a_H} + \frac{1}{K_a^{CH}}\right) \qquad (11)$$

alyzed by using the above equation along with the kinetic pK_a^{CH} obtained from the hydrolysis rates for the esters. In this manner both k_1^{HO} and $k_{-1}^{H_2O}$ could be determined satisfactorily and are also given in Table I. As shown in Table I, values of k_1^{HO} and $k_{-1}^{H_2O}$ determined from measurements at different pH's are in agreement within experimental error, demonstrating that the pK_a values determined kinetically from the rate of ester hydrolysis represent the true pK_a^{CH} values for the ionization of the α-hydrogen of the esters.

An Eigen-type plot[14] for the proton transfer from the α-carbon of 2-cyano-3,3-dimethylbutanoate to hydroxide is given in Figure 3. The pK_a difference between water and carbon acid was used for the *x*-axis coordinate. In

$$dpK_a = pK_a^{H_2O} - pK_a^{CH} \qquad (12)$$

the figure, the proton-transfer rate constants for the *p*-nitrophenyl ester **1** were calcualted by the fitting of the pseudo-first-order rate constants for ester hydrolysis to the log–rate vs. pH profile with eq 4a while the rate constants for the proton transfer for the remaining esters were directly measured. The finding that the data points for the *p*-nitrophenyl and other esters are on the same lines adds credance to the two apparent pK_a equations employed for analysis of the *p*-nitrophenyl ester hydrolytic data.

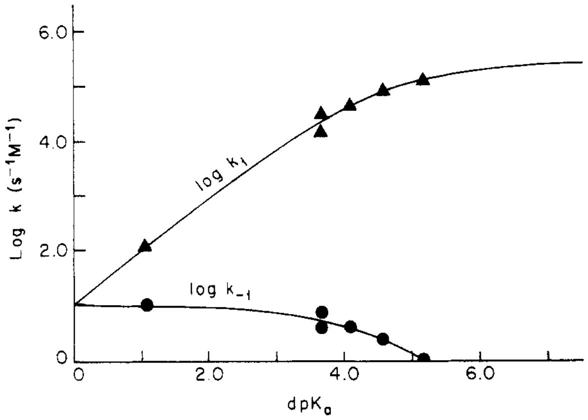

Figure 3. Eigen-type plot (log (k_1^{HO}, $M^{-1} s^{-1}$) and log ($k_{-1}^{H_2O}$, $M^{-1} s^{-1}$) vs. pK_a difference) for proton transfer from 2-cyano-3,3-dimethylbutanoates to hydroxides and from water to the carbanion derived from the ester in aqueous solution at 30 °C and ionic strength 1 M (with KCl). Second-order rate constant for $k_{-1}^{H_2O}$ was calculated by assuming approximate molarity of water to be 53.4 under our experimental conditions.

In the hydrolysis of **1** in the pH region between the two apparent pK_a's ($pK_a^1 < pH < pK_a^2$), reprotonation of the carbanion ($k_{-1}^{H_2O} + k_{-1}^{H}a_H$) is slower than the breakdown of the carbanion into ketene and alkoxide, which means that departure of *p*-nitrophenoxide from the carbanion proceeds more rapidly than carbanion reprotonation. Therefore, carbanion formation is irreversible and the overall hydrolysis mechanism is $(E1cB)_i$. In the pH region below pK_a^1, carbanion formation is reversible and the $(E1cB)_R$ mechanism is operating. At pH values greater than pK_a^2, the carbanion is more stable than the ester and the $(E1cB)_{anion}$ mechanism is controlling. It must be noted that in the pH region near pK_a^{CH} of the esters, the reaction mechanism changes from $(E1cB)_R$ for **2** to $(E1cB)_i$ for **1** by *tert*-butylation. This mechanistic change comes from both the increase of k_2 and decrease of k_{-1} by *tert*-butylation.

The rate constants for proton ionization (k_1^{HO}) are plotted against pK_a^{LG} in Figure 4. Also plotted in Figure 4 are the previously determined[3] second-order rate constants ($k' = k_2K_a^{CH}/K_w$) for E1cB mechanism (eq 2). As can be seen from Figure 4, the rate of ionization (k_1^{HO}) becomes smaller than the apparent second-order rate

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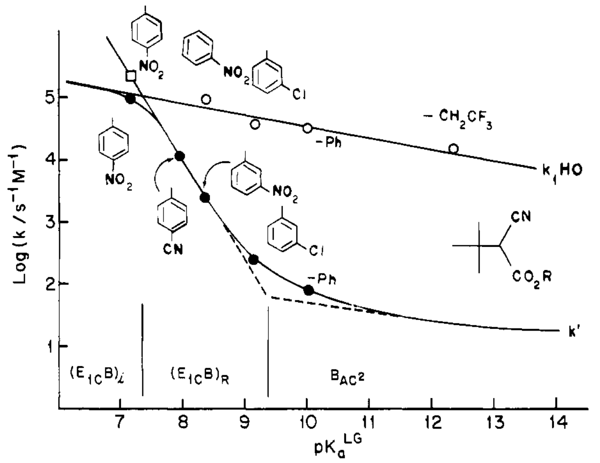

Figure 4. Plots of log (k_1^{HO}, $M^{-1}\ s^{-1}$) vs. pK_a of the conjugate acid of the leaving groups (pK_a^{LG}) for 2-cyano-3,3-dimethylbutanoates together with the rate of the apparent second-order rate constant (k', $M^{-1}\ s^{-1}$) for hydrolytic reaction: (○) rate constant for the proton transfer from 2-cyano-3,3-dimethylbutanoate (carbon acid) to hydroxide (k_1^{HO}, $M^{-1}\ s^{-1}$); (●) apparent second-order rate constant for hydrolytic reaction of 2-cyano-3,3-dimethylbutanoates (k', $M^{-1}\ s^{-1}$). For *p*-nitrophenyl 2-cyano-3,3-dimethylbutanoate, datum was calculated from higher pH region ($8 \le pH \le 9.8$, or segment E in Figure 2B), (for other esters, see ref 3.); (□) apparent second-order rate constant (k', $M^{-1}\ s^{-1}$) for the hydrolysis of *p*-nitrophenyl 2-cyano-3,3-dimethylbutanoate at lower pH region ($4 < pH < 6$, or segment C in Figure 2B).

constant when pK_a^{LG} becomes less than 7.3. (Since $k_1^{HO} < k_2K_a^{CH}/K_w = k_2k_1^{HO}/k_{-1}^{H_2O}$ it follows that $k_{-1} < k_2$ and the ElcB mechanism prevails.) Therefore, in addition to the mechanistic change from $B_{AC}2$ to ElcB found at $pK_a^{LG} = 9.5$,[3] another mechanistic change from $(\mathrm{ElcB})_R$ to $(\mathrm{ElcB})_i$ must occur at $pK_a^{LG} = 7.3$. Inspection of Figure 4 shows that the apprent second-order rate constant for hydrolysis of 1 in the lower pH region (shown by square) is on the same line as the apparent second-order rate constants for hydrolysis of the esters with poorer leaving groups, while the apparent second-order rate constant for hydrolysis of 1 in the higher pH region (shown by black circle) is on the line defined by k_1^{HO} for the esters with poorer leaving groups.

A similar observation of a change in mechanism from $(\mathrm{ElcB})_R$ t $(\mathrm{ElcB})_i$ was made by Williams and his coworkers[15] in a plot of apparent second-order rate constants vs. pK_a^{LG} for the hydrolysis of aryl phenylmethanesulfonates. From the plot, they found that the calculated value of k_2 for their 2,4-dinitrophenyl ester was so large ($>10^{13}$) that the lifetime of the carbanion is less than the vibration frequency. They concluded, therefore, that an "ElcB like E_2" reaction was operating. Their conclusion if faulted, however, by their assumption that the rate constant for spontaneous (i.e., H_2O) reprotonation of the carbanion is diffusion-controlled and by the use of such a constant in the calculation of the rate constant for the departure of the leaving group (k_2). (One should note that in the present study the value of k_2 could be measured directly.) That the spontaneous rate of carbanion protonation cannot be diffusion-controlled is shown by experimental data presented in the same paper. Because their calculated value of pK_a is based on the diffusion-controlled reprotonation of carbanion, it must be incorrect and the rate constant (k_2) for departure of the leaving group from the carbanion must be much smaller than they believe.[16] However, in the same paper, they reported that the hydrolysis of 2,4-dinitrophenyl phenylmethanesulfonate is general-base catalyzed (β = 0.55–0.65; see Figure 6 of their paper) and they also concluded that the rate-determining step is the deprotonation process. Because of microscopic reversibility, protonation of the carbanion must be general-acid catalyzed (α = 0.45–0.35) and, therefore, if proton transfer from water to the carbanion were to be diffusion-controlled ($10^{10}\ s^{-1}$; their assumption!), the rate for proton transfer from HPO_4^- (stronger acid than water) to the carbanion would become greater than $10^{13}\ s^{-1}$. Because they calculated the pK_a value of the carbon acid, based on the diffusion-controlled reprotonation of the carbanion, the pK_a value must be incorrect and the value of k_2 (departure of the leaving group from the carbanion) must be much smaller than they believe.[16]

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