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General Base Catalysis of Ester Hydrolysis[1]

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Abstract: The hydrolysis of alkyl formates with leaving groups in the range $pK_a = 12–16$ is catalyzed by substituted acetate anions. There is an increase in the Brønsted β value for general base catalysis with decreasing pK_a of the leaving alcohol and a complementary increase in $-\beta_{lg}$ with decreasing pK_a of the catalyzing base, both of which are consistent with a value of $p_{xy} = \partial\beta/-pK_{1g} = \partial\beta_{lg}/-\partial pK_{BH} \simeq 0.11$. This result supports a class n mechanism of general base catalysis, in which a proton is abstracted from the nucleophilic water molecule by the base catalyst in the transition state; it is not consistent with the kinetically equivalent class e mechanism of electrophilic catalysis by general acids of a reaction with hydroxide ion, by proton donation to the leaving alcohol. Solvent deuterium isotope effects in the range $k_{H_2O}/k_{D_2O} = 3.6–5.3$ for the buffer-independent reaction and 2.5–2.8 for catalysis by CH_3COO^- support concerted proton transfer and O–C bond formation. The secondary isotope effect for catalysis of the hydrolysis of LCOOMe by acetate ion is $k_D/k_H = 1.05$. Both nucleophilic and general base mechanisms of catalysis by acetate anions are observed for the hydrolysis of substituted phenyl formates with leaving groups of $pK_a = 7.1–10.1$. A small value of $\beta = 0.12$ for general base catalysis of the hydrolysis of phenyl formate and *p*-methylphenyl formate represents catalysis of the addition of water by hydrogen bonding of water to the base catalyst. On the other hand, a larger value of $\beta = 0.35$ and a decrease in k_{H_2O}/k_{D_2O} to 1.2 were observed for general base catalysis of the hydrolysis of *p*-nitrophenyl formate. It is suggested that the increase in β with decreasing pK_{lg} (an apparent "anti-Hammond effect") may be accounted for by a change in mechanism, from catalysis of a stepwise reaction of phenyl and *p*-methylphenyl formates to concerted general base catalysis of formyl transfer to water for the reaction of *p*-nitrophenyl formate.

Introduction

Bases can bring about the hydrolysis of esters by nucleophilic catalysis and by general base catalysis.[2–4] Nucleophilic attack by hydroxide ion gives the hydrolysis products directly, while nucleophilic attack by pyridines and imidazole forms a cationic acylated amine that reacts rapidly with water.[5] However, at neutral pH, the rate of hydrolysis of most esters is very slow; the half-life for the uncatalyzed hydrolysis of ethyl acetate in water at 25 °C is approximately 89 years.[6] Nucleophilic catalysis by tertiary amines of the hydrolysis of most alkyl esters is insignificant or very slow. If an addition intermediate is formed, it expels the amine much more rapidly than the alkoxide leaving group, and the acylated amine is formed very slowly.

However, amines and other bases can also catalyze hydrolysis by removing a proton from a molecule of water or alcohol as it attacks an acyl compound, by general base catalysis.[7,8] This provides a mechanism by which enzymes can catalyze acyl transfer reactions; it is the mechanism by which the imidazole group of serine hydrolases facilitates attack of the serine hydroxyl group on esters and amides and attack of water on the acyl enzyme.[7–9] General base catalysis has been observed for the methanolysis of acyl-substituted *p*-nitrophenyl acetates and for the hydrolysis of acetylimidazole and esters with poor leaving groups, but the mechanism of catalysis of the hydrolysis of aliphatic esters has not been examined in detail.[2–4]

We describe here a study of catalysis of the hydrolysis of alkyl and aryl esters by buffer bases. Formate esters were chosen for examination because they undergo hydrolysis at an easily measurable rate at neutral pH and ordinary temperatures. The reactions of substituted phenyl formates were followed spectrophotometrically, and the initial rates of hydrolysis of alkyl formates were followed by determining the concentration of formate product with the enzyme formate dehydrogenase.

Experimental Section

Materials. Substituted phenyl formates were obtained as described previously.[10] Alkyl formates were prepared by refluxing formic acid with a 4–5-fold molar excess of alcohol for 12–15 h followed by distillation of the ester product through a Vigreux column. All esters were purified by fractional distillation from P_2O_5. Ethyl formate, methyl formate, and $DCOOCH_3$ (98 atom % D), obtained from Aldrich Chemical Co., were distilled before use. Yeast formate dehydrogenase and NAD (Li salt, formate free) were from Boehringer-Mannheim.

Kinetics. The initial rates of hydrolysis of substituted phenyl formate esters were determined at 25 °C and an ionic strength of 1.0 M (KCl). Rate constants for buffer catalysis of the hydrolysis of substituted phenyl formates were determined spectrophotometrically by following the release of the phenol product with a Perkin-Elmer Lambda 4B spectrophotometer at an appropriate wavelength: *p*-nitrophenol, 330 nm; *m*-nitrophenol, 350 nm; phenol, 270 nm; and *p*-methylphenol, 285 nm. Reactions were initiated by the addition of ester in acetonitrile to give an initial concentration of 0.5-3.0 mM; each reaction solution contained 1% acetonitrile.

Rate constants for buffer catalysis of the hydrolysis of substituted alkyl formates, 5–10 mM, were determined by following the disappearance of ester or the release of formic acid with time. Rate determinations in cacodylate and acetate buffers were carried out at seven different concentrations of buffer, 50% anion, in the range 0–1.0 M. Rate constants for catalysis by methoxyacetate and cyanoacetate anions were determined in a buffer of 0.02 M MES (morpholineethanesulfonic acid) at pH 5.5.

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[2] Dawson, H. M.; Lowson, W. *J. Chem. Soc.* **1929**, 393–401.

[3] Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *81*, 1743–1750.

[4] Gold, V.; Oakenfull, D. G.; Riley, T. *J. Chem. Soc. B* **1968**, 515–519.

[5] Bender, M. L.; Turnquest, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1652, 1656. Bruice, T. C.; Schmir, G. L. *J. Am. Chem. Soc.* **1957**, *79*, 1663–1667. Brouwer, D. M.; Vlugt, M. J.; Havinga, E. *Proc. K. Ned. Akad. Wet.* **1957**, *B60*, 275.

[6] Skrabal, A. *Trans. Faraday Soc.* **1928**, *24*, 687–696.

[7] Anderson, B. M.; Cordes, E. H.; Jencks, W. P. *J. Biol. Chem.* **1961**, *236*, 455–463.

[8] Jencks, W. P.; Carriuolo, J. *J. Biol. Chem.* **1959**, *234*, 1280–1285.

[9] Barnard, E. A.; Stein, W. D. *Adv. Enzymol. Relat. Subj. Biochem.* **1958**, *20*, 51. Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2* **1987**, 159–167. Neuvonen, H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 669–673.

[10] Stefanidis, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1993**, *115*, 1650–1656.

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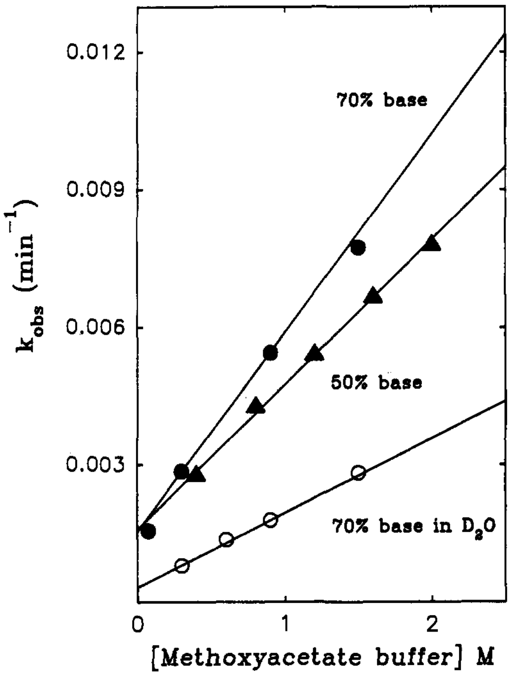

Figure 1. Dependence on the concentration of methoxyacetate buffers of the pseudo-first-order rate constants for the hydrolysis of *p*-methylphenyl formate at 25 °C, ionic strength 1.0 (KCl).

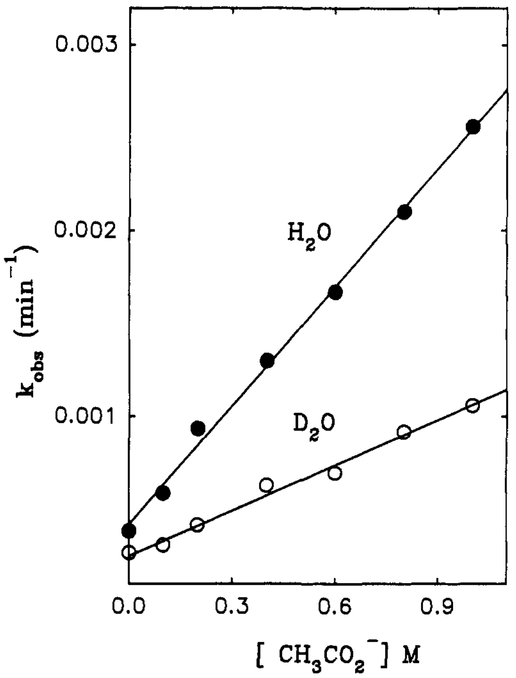

Figure 2. Dependence on the concentration of acetate anion of k_{obs} for the hydrolysis of 1,1-dichloroethyl formate in H_2O and D_2O at 25 °C, ionic strength 1.0 (KCl).

The individual reactions were carried out in vials that were sealed with a Teflon cap. The kinetic procedure was similar to that of Jencks and Carriuolo.[3] Aliquots of ester were withdrawn from the vial at intervals with a Hamilton gastight syringe (50-μL) and added to a mixture of 0.93 mL of 3.09 M KOH, 0.75 mL of 4 M $NH_2OH{\cdot}HCl$, and 0.3 mL of 2 M TRIS in a 10-mL test tube sealed with a rubber septum. After the mixture was incubated for 15–20 min, the rubber septum was removed and 4 mL of 10% $FeCl_3{\cdot}6H_2O$ in 1 N HCl was added. The mixture was stirred for 30 s, and the absorbance of the hydroxamic acid–Fe^{3+} complex was measured at 540 nm 2 min after the addition of $FeCl_3{\cdot}6H_2O$.

Alternatively, the rates of release of formic acid were determined with formate dehydrogenase, essentially as described by Cleland et al.[11] Aliquots (2–3 μL) were withdrawn from the reaction vial at intervals with a Hamilton syringe and injected into 1.0 mL of a solution containing 4.2×10^{-3} M NAD, 0.03 M HEPES buffer (pH = 7.0), 1 unit of yeast formate dehydrogenase, and 35% DMSO (v/v). The absorbance at 340 nm was recorded after 5 min. Pseudo-first-order rate constants k_{obs} were obtained from least-squares slopes of plots of $\ln(A_\infty - A_t)$ against time, which were linear for ≥3 half-lives.

First-order rate constants for the slow hydrolysis of 0.1 M propargyl formate, methyl formate, and ethyl formate were determined with formate dehydrogenase by dividing the *initial* rate of formation of formic acid by the concentration of ester. The total concentration of ester, usually 0.1 M, was measured by hydrolyzing an aliquot of the ester solution at high pH and then determining the concentration of formic acid with formate dehydrogenase.

Solvent deuterium isotope effects for catalysis of the hydrolysis of formate esters by acetate anion were determined from rate constants at six to eight buffer concentrations, 50% anion, in the range of 0–1.0 M in H_2O and D_2O.

Results

Hydrolysis of formate esters follows the rate law of eq 1, in which k_w is the first-order rate constant for pH-independent hydrolysis and k_b is the second-order rate constant for catalysis of hydrolysis by a buffer base. Figure 1 shows a typical example

$$k_{obs} = k_a[H^+] + k_w + k_{OH}[HO^-] + k_b[B] \qquad (1)$$

of catalysis of the hydrolysis of *p*-methylphenyl formate by methoxyacetate buffers in water and deuterium oxide. The observed first-order rate constants increase linearly with increasing buffer concentration; there is no indication of upward curvature that would suggest a third-order term for catalysis by buffer base and acid. The increase in slope with increasing fraction of buffer base indicates general base catalysis of ester hydrolysis. The buffer-independent rates of hydrolysis, obtained by extrapolation of the observed rate constant to zero buffer concentration, were found to show no significant variation in the range of pH = 2.0–6.2. Both the slope k_b and the intercept k_w are decreased in deuterium oxide, with solvent isotope effects of $k_{H_2O}/k_{D_2O} = 5.3$ and $k_b(H_2O)/k_b(D_2O) = 2.6$.

Values of k_w for the pH-independent hydrolysis of alkyl formates in 1 M KCl were determined in the absence of added buffers. Hydrolysis was accompanied by a small decrease in pH under these conditions; however, the change in pH did not affect the rate of hydrolysis because plots of $\ln(A_\infty - A_t)$ against time were linear for 2–3 half-lives. The measured values of k_w were found to be identical with those obtained from extrapolations of buffer dilution plots. Catalysis of hydrolysis by the solvated proton was observed for propargyl formate, methyl formate, and ethyl formate at pH < 3, but values of k_{H^+} were not determined.

Figure 2 shows typical data for catalysis by acetate buffers of the hydrolysis of an alkyl formate, 1,1-dichloroethyl formate, in water and deuterium oxide. Both the slope and intercept are decreased in D_2O, with solvent isotope effects of $k_{H_2O}/k_{D_2O} = 1.6$ for k_w and 2.6 for k_b.

The rate constants k_w and k_b for hydrolysis of phenyl formates and alkyl formates are collected in Tables I and II, respectively. Rate constants for hydrolysis of several formate esters in deuterium oxide and the solvent kinetic deuterium isotope effects for these reactions are also given in the tables. The secondary deuterium isotope effect for catalysis by acetate ion of the hydrolysis of HCOOMe and DCOOMe was found to be $k_D/k_H = 1.05$ from determinations of rate constants in the presence of eight concentrations of acetate buffer, 90% anion, in the range of 0.1–1.0 M. Rate constants k_a for catalysis by a proton were not determined.

Discussion

Mechanisms of Acetate-Catalyzed Hydrolysis of Substituted Phenyl Formate Esters. Hydrolysis of substituted phenyl formates

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(11) Hermes, J. D.; Morrical, S. W.; O'Learly, M. H.; Cleland, W. W. *Biochemistry* **1984**, *23*, 5479–5488.

Table I. Second-Order Rate Constants for General Base Catalysis of the Hydrolysis of Phenyl Formates HCOOR from Phenols at 25 °C and Ionic Strength 1.0 (KCl)

	10^2k_2 (M^{-1} min^{-1}), R (pK_a)				
catalyst	*p*-methoxyphenyl (10.2)	*p*-methylphenyl (10.1)	phenyl (9.9)	*m*-nitrophenyl (8.2)	*p*-nitrophenyl (7.2)
cacodylate		35	81	4600	17000
k_{D_2O}		42			
acetate	1.1	1.3	1.4	15	79
k_{D_2O}	0.44		0.65	11	67
k_{H_2O}/k_{D_2O}	2.5		2.2	1.4	1.2
3-chloropropionate		0.72	0.65	7.4	24
methoxyacetate		0.62	0.62	3.0	8.0
k_{D_2O}		0.24			4.1
k_{H_2O}/k_{D_2O}		2.6			2.0
chloroacetate			0.47	2.7	6.1
cyanoacetate		0.46	0.42	1.8	3.3
k_{D_2O}					1.70
difluoroacetate				1.5	
H_2O^a	0.0020	0.0032	0.0036	0.027	0.063
D_2O^a	0.00047	0.0006	0.00085	0.0074	0.017
k_{H_2O}/k_{D_2O}	4.2	5.3	4.2	3.6	3.7

[a] $k_2 = k_0/55.5$ M (k_0 is the first-order buffer-independent rate constant).

Table II. Second-Order Rate Constants for General Base Catalysis of the Hydrolysis of Alkyl Formates HCOOR at 25 °C and Ionic Strength 1.0 (KCl)

	10^3k_b (M^{-1} min^{-1}), R					
catalyst	CH_2-C_2H_5	CH_2-CF_3	CH_2-$CHCl_2$	CH_2-$C\equiv CH$	CH_2-CH_2Cl	CH_2-CH_3
cacodylate		43		9.2		1.2
acetate	4.8	5.5	2.1	1.2	0.95	0.16
in D_2O	1.7		0.81			0.065
k_{H_2O}/k_{D_2O}	2.8		2.6			2.5
methoxyacetate	2.6	2.1	0.64	0.29	0.19	
cyanoacetate	0.71	0.72	0.22	0.08		
H_2O^a	0.0045	0.008	0.0073	0.0014	0.0020	0.00023
D_2O^a	0.0036		0.0045			0.000075
k_{H_2O}/k_{D_2O}	1.3		1.6			3.0

[a] $k_b = k_0/55.5$ M (k_0 is the buffer-independent rate constant).

Table III. Brønsted β and β_{lg} Coefficients for Base-Catalyzed Hydrolysis of Substituted Phenyl Formates

leaving group	pK_{lg}	$\beta_1{}^a$	$\beta_2{}^a$
p-methylphenol	10.09	0.1	1.2
phenol	9.86	0.1	1.4
m-nitrophenol	8.19	0.3	1.9
p-nitrophenol	7.15	0.35	1.6

catalyst	pK_a	$\beta_{lg}{}^b$
cacodylate	6.16	-1.1
acetate	4.65	-0.62
3-chloropropionate	3.93	-0.55
methoxyacetate	3.40	-0.39
chloroacetate	2.70	-0.42
cyanoacetate	2.23	-0.32
water	-1.74	-0.46

[a] Derived from a fit to eq 2 (see text). [b] See Figure 4.

with leaving groups of pK = 7–10 is catalyzed by substituted acetate anions and cacodylate anion. Figure 3 shows the dependence of log k_2 upon the pK_a of the base catalyst. The plots follow nonlinear Brønsted correlations that can be fitted to eq 2 with the parameters β_1 = 0.12–0.35 for catalysis by weak bases ($pK < 3$) and β_2 = 1.2–1.9 for catalysis by stronger bases ($pK > 4$).

$$\log k_b = \beta_1 pK_a + C_1 + \beta_2 pK_a + C_2 \qquad (2)$$

Figure 4 and Table III show that these changes in β_1 and β_2 are paralleled by changes in the value of $-\beta_{lg}$. The values of $-\beta_{lg}$

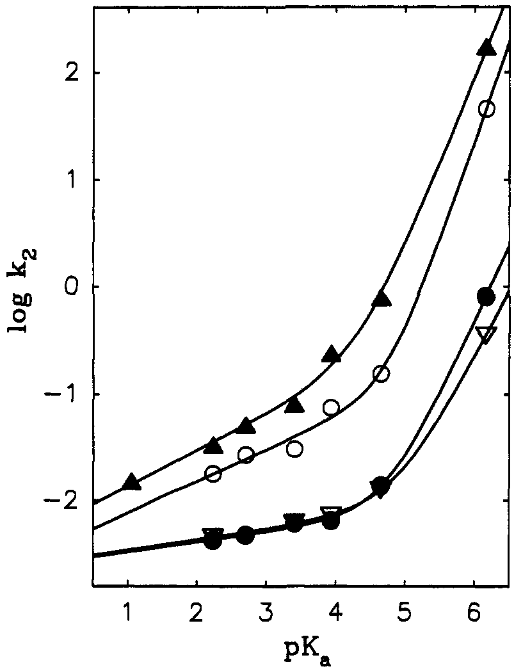


Figure 3. Dependence of log k_2 for the hydrolysis of phenyl formates on the pK_a of the base catalyst: (PNPF, ▲) *p*-nitrophenyl formate, (MNPF, ○) *m*-nitrophenyl formate, (PF, ●) phenyl formate, and (PMPF, △) *p*-methylphenyl formate. The curves are fit to eq 2.

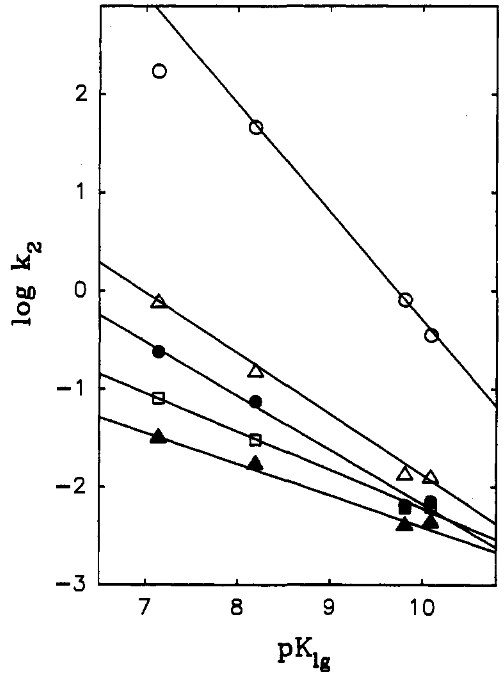


Figure 4. Dependence on pK_{lg} of log k_2 for the hydrolysis of phenyl formates catalyzed by substituted acetate and cacodylate anions: (○) cacodylate, (△) acetate, (●) 3-chloropropionate, (□) chloroacetate, and (▲) cyanoacetate.

increase from 0.3 for catalysis by cyanoacetate anion to 1.1 for catalysis by cacodylate anion.

These changes represent a large *increase* in the selectivity of the reaction with increasing reactivity, which is the opposite of what is expected from a change in the structure of the transition state when the activation barrier of a reaction decreases. A change in the rate-limiting step of a single reaction mechanism with increasing pK_a of the nucleophile results in a smaller reaction rate and a downward break in a structure–reactivity correlation, while an increase in rate above that predicted for one reaction

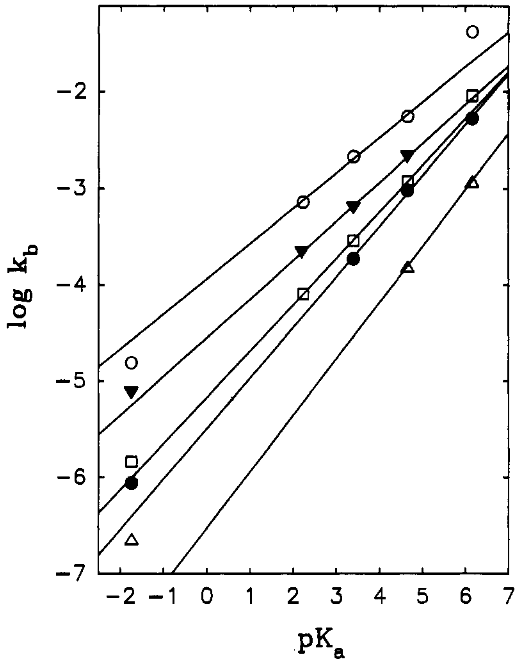


Figure 5. Brønsted plots for the dependence of log k_b on the pK_a of the base catalyst for general base catalysis of the hydrolysis of alkyl formates: (○) trifluoroethyl formate, (▼) 1,1,-dichloroethyl formate, (□) propargyl formate, (●) chloroethyl formate, and (△) ethyl formate.

mechanism occurs when the reaction follows a different mechanism that has a larger dependence on the structure of the nucleophile.

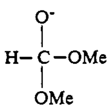
The large increases in the Brønsted β and $-\beta_{lg}$ values with increasing basicity of the catalysts are accompanied by decreases in the solvent deuterium isotope effect. The solvent isotope effect for catalysis of the hydrolysis of *p*-nitrophenyl formate decreases from k_{H_2O}/k_{D_2O} = 2.0 for catalysis by methoxyacetate and cyanoacetate anions to 1.2 for catalysis by acetate anions. The solvent isotope effects for the buffer-independent "water" reaction, in the range k_{H_2O}/k_{D_2O} = 3.6–5.3, are even larger.

The large values of β and $-\beta_{lg}$ and the small solvent deuterium isotope effects for basic catalysts, such as cacodylate anion, are characteristic of a nucleophilic mechanism of catalysis. On the other hand, the small values of β and $-\beta_{lg}$ and the significant solvent deuterium isotope effects for catalysis by weakly basic catalysts, such as cyanoacetate anion, and for the buffer-independent reaction with water are characteristic of concerted general base catalysis, in which proton transfer from water to the base catalyst accompanies and facilitates bond formation and cleavage at carbon.[3] Therefore, we conclude that the observed nonlinear Brønsted plots describe a change in the reaction mechanism from predominantly nucleophilic catalysis for bases of p$K > 5$ to general base catalysis for bases of p$K < 3$ and for the water reaction, which presumably involves proton transfer from the attacking water molecule to a second water molecule in the transition state. Both mechanisms contribute significantly to the observed catalysis of hydrolysis with acetates and leaving groups of intermediate basicity.

There is also a systematic increase in the magnitude of the solvent deuterium isotope effect for general base catalysis of the hydrolysis of substituted phenyl formates as the leaving group becomes more basic and less reactive (Table I). Catalysis by acetate anion exhibits an increase in the solvent deuterium isotope effect from k_{H_2O}/k_{D_2O} = 1.2 for the reaction of *p*-nitrophenyl formate (pK_{lg} = 7) to k_{H_2O}/k_{D_2O} = 2.5 for *p*-methoxyphenyl formate (pK_{lg} = 10.1). This increase confirms a change in mechanism from nucleophilic to general base catalysis by acetate ion with increasing pK of the leaving group. For hydrolysis catalyzed by substituted acetate anions, the change to general base catalysis occurs when the pK of the leaving group is ≈10. However, the small solvent deuterium isotope effect of k_{H_2O}/k_{D_2O} = 1.4 for the reaction of acetate ion with *m*-nitrophenyl formate (Table I) suggests that this reaction involves nucleophilic as well as general base catalysis. A similar change in mechanism from nucleophilic to general base catalysis with increasing pK of the leaving group has been observed for the acetate-catalyzed hydrolysis of substituted-phenyl acetates by Gold and co-workers.[4] These reactions follow predominantly general base catalysis when the pK of the leaving group is ≥8.0. The relatively small acyl group and the absence of hyperconjugation in formate esters favor nucleophilic substitution so that the change from nucleophilic to general base catalysis occurs with a higher pK_a of the leaving group for formyl than for acetyl esters.

Mechanism of General Base Catalysis of Hydrolysis of Alkyl Formates. Catalysis by substituted acetate anions is observed for the hydrolysis of alkyl formates that have leaving groups with pK_a in the range 12.4–16. Catalysis by acetate ion is decreased 2.5- to 2.8-fold in D_2O compared with H_2O (Table II), and the Brønsted slopes (Figure 5) are in the range β = 0.36–0.58. The solvent deuterium isotope effect and the values of β, which are much smaller than the values of β in the range 1.2–1.9 for nucleophilic reactions with substituted phenyl formates (Table III), support a mechanism of general base catalysis in which the transition state is composed of three molecules: water, ester, and acetate anion.

Several kinetically equivalent mechanisms are consistent with the observed stoichiometry of the transition state. These include fully concerted mechanisms with no intermediate and stepwise mechanisms that proceed through a tetrahedral addition intermediate. Capon and co-workers[12] have shown that the anionic tetrahedral addition intermediate **1** expels methoxide ion to give methyl formate with a rate constant of 3.7 × 10⁷ s⁻¹ at 15 °C; the uncharged intermediate is much more stable; it is cleaved with a rate constant of 0.73 s⁻¹. Therefore, a fully concerted mechanism of proton transfer and leaving group expulsion is unlikely in these reactions because the addition intermediate has a significant lifetime.



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Six kinetically equivalent mechanisms for general base catalysis of the hydrolysis of alkyl formates proceed through transition states 1–6. There are two fully concerted mechanisms, 1 and 3, and four stepwise mechanisms, 2 and 4–6. Transition states 1–4

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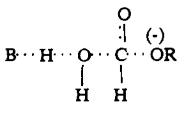

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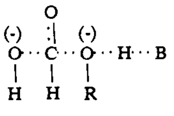

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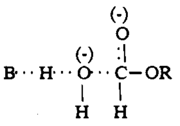

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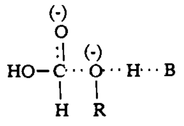

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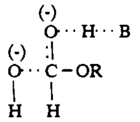

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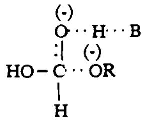

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[12] Capon, B.; Ghosh, A. K. *J. Am. Chem. Soc.* **1981**, *103*, 1765–1768.

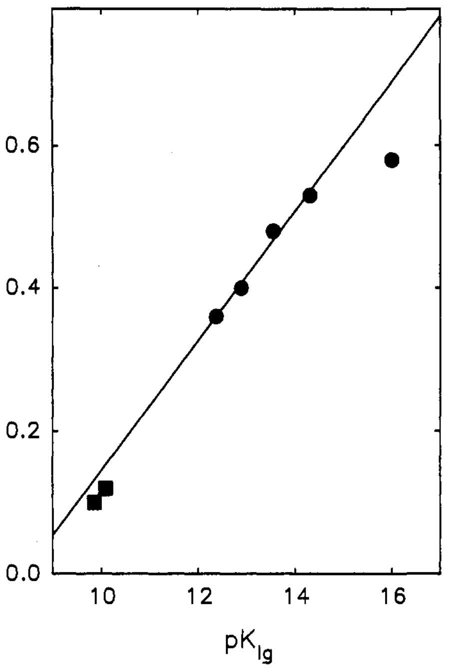

Figure 6. Dependence of the Brønsted β coefficient on the pK_a of the leaving group for general base catalysis of the hydrolysis of alkyl formates (●) and phenyl formates (■).

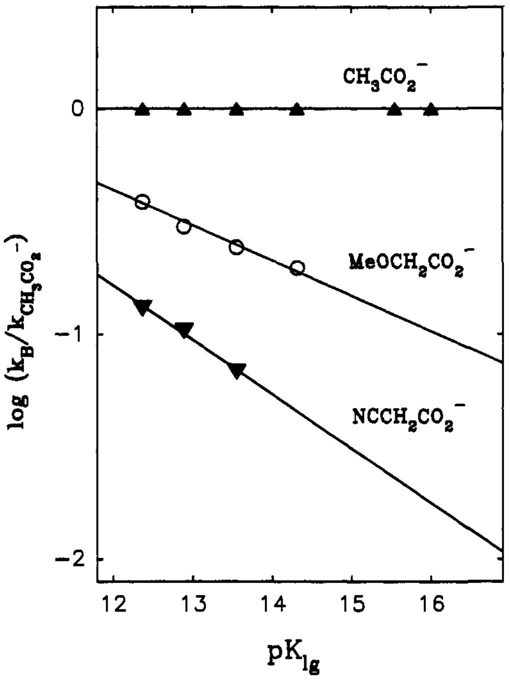

Figure 7. Dependence of log k_b on the pK_a of the leaving alcohol for general base catalysis of the hydrolysis of alkyl formates by acetate (○), methoxyacetate (▼) and cyanoacetate anions (△) and by water (●).

represent class n mechanisms, in which the catalyst abstracts a proton from the attacking water molecule or donates a proton to the leaving alcohol, which is the nucleophile when the reaction proceeds in the reverse direction. Transition states 5 and 6 represent class e mechanisms, in which proton donation provides electrophilic catalysis to stabilize the transition state.[13]

Figures 5–8 and Table IV show the changes in the Brønsted coefficient for general base catalysis with changing pK_a of the leaving group, $\partial\beta/\partial pK_{lg}$, and the complementary changes in the dependence of log k on the pK_a of the leaving group, β_{lg}, with changing pK_a of the catalyst, $\partial\beta_{lg}/\partial pK_{BH}$. These indicators of changing transition state structure are related by the interaction coefficient p_{xy}, as described by eq 3.[13]

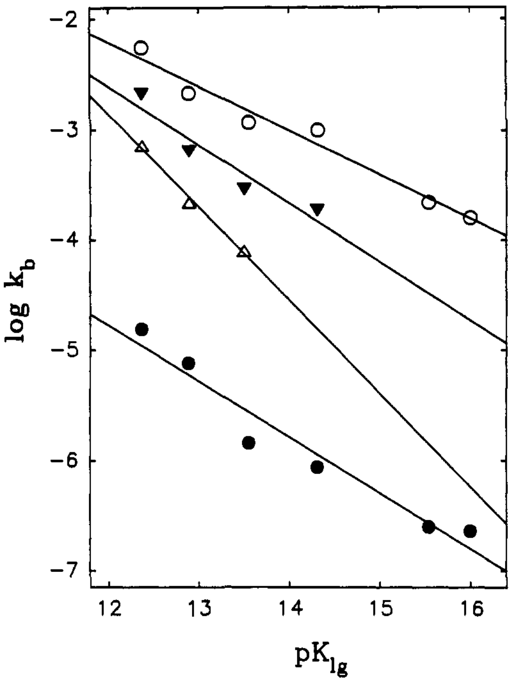

Figure 8. Logarithmic plots showing the dependence of the ratios of rate constants for catalysis of the hydrolysis of alkyl formates by different bases on the pK_a of the leaving alcohol.

Table IV. Brønsted β and β_{lg} Coefficients for General Base Catalysis of the Hydrolysis of Alkyl Formates HCOOR

R	β	pK$_{lg}$
CF_3CH_2–	0.36	12.4
Cl_2CHCH_2–	0.40	12.8
$HCCH_2$–	0.48	13.6
$ClCH_2CH_2$–	0.53	14.3
CH_3CH_2–	0.58	16.0
catalyst	β_{lg}	pK$_a$
acetate	–0.40	4.7
methoxyacetate	–0.53	3.4
cyanoacetate	–0.85	2.2
water	–0.51	-1.7

$$p_{xy} = \frac{\partial\beta}{\partial pK_{lg}} = \frac{\partial\beta_{lg}}{\partial pK_{BH}} \qquad (3)$$

Figures 5 and 6 and Table IV show that the Brønsted coefficient β for general base catalysis of the hydrolysis of alkyl formates by substituted acetate ions increases from 0.36 to 0.58 as the pK_a of the leaving group increases from 12.4 to 16. This increase indicates that there is more proton abstraction from the attacking water molecule by the base catalyst in the transition state for hydrolysis of less reactive esters. The slope of the line in Figure 6 corresponds to an interaction coefficient of $p_{xy} = 0.11$. It is possible that the negative deviation of the β value for catalysis of the hydrolysis of ethyl formate (pK_{lg} = 16) represents a partial change in the rate-limiting step with this poor leaving group. The β values for catalysis of the reactions with phenyl formate and *p*-methylphenyl formate (squares) fall close to the correlation line for alkyl esters. There is no indication that the transition state is perturbed by imbalance between proton transfer and development of negative charge on the phenolate anion as a result of resonance delocalization into the aromatic ring. Resonance delocalization may not be expressed in transition states in proportion to the amount of bond breaking, as in the "nitroalkane anomaly".[13]

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[13] Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511–527.

Figure 7 shows the complementary increase in $-\beta_{lg}$, the dependence of log k on the pK of the leaving group, from 0.40 to 0.85, with decreasing pK_a of the base catalyst. This increase in selectivity with decreasing reactivity is shown more clearly by the ratio plots of $\log(k_B/k_{AcO^-})$ in Figure 8.

These changes in structure–reactivity coefficients indicate that as the basicity of the catalyst decreases, there is more bond formation to the attacking water molecule and more weakening of the bond to the leaving group in the transition state. The better fit of the data in Figure 8 suggests that much of the scatter in Figure 7 may be caused by uncertainty in the values of pK_{lg} rather than in those of log k. The smaller value of $-\beta_{lg} = 0.51$ for the reaction with water in the absence of a base catalyst presumably reflects the absence of a net negative charge in the transition state for the water reaction. Electron-withdrawing substituents on a weakly basic catalyst would be expected to stabilize this negative charge and increase log k with a corresponding increase in $-\beta_{lg}$.

The direction of the changes in transition-state structure with changing structure of the reactants and catalysts can be used to distinguish between several different reaction mechanisms that are consistent with the observed rate law.[13] The observed changes in structure–reactivity coefficients support a class n mechanism, 1 or 2, in which the base catalyst abstracts a proton from the attacking water molecule in the rate-limiting step. An ester with a poor leaving group, with a high pK_a, is relatively unreactive because electron donation from the leaving group stabilizes the ester and decreases the rate of leaving group expulsion; therefore, the rate of its hydrolysis is expected to show a larger dependence on the strength of the nucleophile for its hydrolysis. General base catalysis increases the nucleophilicity of the attacking group by partial removal of a proton so that more proton removal from the attacking water molecule and a larger β value are expected in the transition state for reaction of an ester with a more basic leaving group. It follows from eq 3 that the dependence of log k on the pK_a of the leaving group, $-\beta_{lg}$, increases with increasing basicity of the base catalyst; the amount of this change is described by the interaction coefficient p_{xy}.

Changes of structure–reactivity coefficients in the opposite direction are expected for catalysis of methyl formate hydrolysis by mechanisms 3–6, which are kinetically equivalent to mechanisms 1–2. In these mechanisms, the reaction with hydroxide ion is facilitated by general acid catalysis of leaving group expulsion (mechanisms 3 and 4) or by stabilization of the negative charge on the carbonyl oxygen atom in the transition state (mechanisms 5 and 6).[13]

Mechanisms 3 and 4 are also class n reactions. Mechanisms 3 and 4 are equivalent to mechanisms 1 and 2 in the opposite direction except that the catalysis involves transfer of a proton to or from the substituted alcohol in the two directions, instead of to or from water. However, in these mechanisms, the proton that is transferred from the catalyst is much closer to substituents on the leaving group.

In a class n mechanism, the Brønsted β value for general base catalysis increases with decreasing pK_a of the attacking alcohol, as described by the p_{xy} coefficient of eq 4.[13,14] This is equivalent to an increase in α with increasing pK of the nucleophile for the reaction in the reverse direction, in which the nucleophile has become the leaving group and is expelled with general acid catalysis.

$$p_{xy'} = \frac{\partial\beta}{-\partial pK_{nuc}} = \frac{\partial\beta_{nuc}}{-\partial \mathrm{p}K_{BH^+}} = \frac{\partial\alpha}{\partial pK_{lg}} \tag{4}$$

Mechanisms 5 and 6 are class e reactions, in which a Brønsted acid catalyzes the nucleophilic attack of hydroxide ion on the ester or the expulsion of the leaving group by partial proton donation to the carbonyl oxygen atom in the transition state. This proton donation will accelerate the reaction by stabilizing the anionic addition intermediate and the partial negative charge in the transition states for its formation and its breakdown. Reactions of this kind show the opposite structure–reactivity behavior, a decrease in β with an increase in the pK_a of the leaving group (note that 5 and 6 are essentially the same mechanism, except for the replacement of HO^- by RO^- as the leaving group).[13,14] An increase in the pK_a of the leaving group results in a decrease in reactivity of the ester and a corresponding increase in proton donation to the carbonyl oxygen atom to stabilize the transition state. This represents an increase in the Brønsted α value and a decrease in the observed β value (the observed general base catalysis is kinetically equivalent to general acid catalysis of a reaction with hydroxide or alkoxide ion).[13,14]

We conclude that general base catalysis of the hydrolysis of methyl formate occurs by rate-determining removal of a proton from the attacking water molecule according to mechanism 2.

The rate constants for the water reaction (pK_a = −1.7) do not follow the trend of the correlations in Figures 5 and 7. This may be accounted for by an electrostatic effect of the negative charge on the catalyst. The negative charge in the transition state for catalysis by acetate anions will be stabilized by electron-withdrawing substituents in the ester. This results in an increased rate and an increased sensitivity of the rate to polar substituents.

The large solvent isotope effects for the water reaction of substituted phenyl formates, in the range of $k_{H_2O}/k_{D_2O} = 3.6$–5.3 (Table I), indicate that proton transfer is concerted with O–C bond formation in the rate-limiting transition state of this reaction. There is little, if any, thermodynamic driving force for this proton transfer because the acidity of a water molecule that is attacking the carbonyl group in the transition state is expected to be smaller or similar compared with that of H_3O^+. The fact that large isotope effects are observed suggests that a considerable amount of bond formation has developed between the attacking water molecule and the carbonyl carbon atom in the transition state so that the pK_a of the attacking water molecule is greatly decreased and proton transfer is nearly isoenergetic. Proton transfers between electronegative atoms that are thermodynamically favorable have little or no barrier and are diffusion-controlled, while the corresponding proton transfers that are thermodynamically unfavorable are limited by diffusion-controlled separation of the products.

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(14) Sørensen, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4675–4690. Euranto, E. K.; Kanerva, L. T.; Nurmi, U. *Acta Chem. Scand. Ser. B* **1986**, *40*, 337–342.