Irradiation of *cis*-3,3-Dimethyl-1,4-hexadiene (10) in the Presence of 12. A solution of **10** (40 mg) and the rhodium complex **12** (8 mg) in pentane (15 ml) was irradiated (254 nm). The reaction mixture gradually deposited an orange-yellow solid on the walls of the quartz vessel, and the solution went from yellow to colorless over a period of 49 hr. The resulting solution contained *cis*-1,4-diene **10** (89%) and *trans*-1,4-diene **11** (11%).

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(1) Freshman undergraduate research participant.
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Nonlinearity in Buffer-Rate Relationships. The Significance of Carboxylate-Acid Complexes[1]

Elli Smakula Hand[2] and William P. Jencks*

Contribution No. 1036 from the Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. *Received January 24, 1975*

Abstract: The observed rate constants for nitroethane ionization increase linearly with acetate buffer concentration up to 2 *M* when the ionic strength is maintained at 2.0 *M* with potassium trifluoroacetate. A small upward curvature when the ionic strength is maintained with potassium nitrate is attributed to a specific salt effect. A larger upward curvature for cyclohexanone enolization is found with both trifluoroacetate and nitrate and is attributed to bifunctional acid-base catalysis. No evidence for buffer association was found for these reactions. However, plots of observed rate constants against formate buffer concentrations of up to 2 *M* for the reaction of formate with iodine and for the protonation of nitroethane anion exhibit downward curvature that can be accounted for by the formation of an unreactive $(HCOOH{\cdot}OOCH)^-$ anion with an association constant $K_{12} = 0.25\ M^{-1}$. The hydrolysis of benzylhydrylidenedimethylammonium ion exhibits "negative catalysis" by formic acid that can be accounted for by the decrease in water concentration in concentrated buffer solutions if it is assumed that four water molecules are required for water-catalyzed hydrolysis. Other causes of nonlinear plots of rate against buffer concentration are illustrated and discussed.

A break in a plot of rate against buffer concentration that is caused by a change in rate-determining step is one of the most useful results that can be obtained from kinetic experiments because such a break demonstrates that the reaction must proceed through at least two steps and an intermediate. The identification of such a break is usually straightforward when it occurs at low buffer concentration at a constant ionic strength and pH, but curvature in plots of rate against buffer concentration is more difficult to interpret in concentrated buffer solutions because buffer complexation and other factors can also give rise to curvature. The experiments reported here were undertaken after the appearance of several reports describing a nonlinear dependence of rate on the concentration of acetate and formate buffers, in the hydrolysis of ketene acetals and lactonization, that was attributed to the formation of inactive

$(RCOOH{\cdot}OOCR)^-$ and $(RCOOH)_2$ complexes with association constants in the range 0.4-1.6 M^{-1} in concentrated aqueous buffer solutions.[3,4] More recently it has been pointed out that it is likely that the nonlinear dependence on buffer concentration in these reactions is caused by a change in rate-determining step.[5] In view of the importance of this kinetic criterion for a change in rate-determining step and our experience that catalysis of the dissociation of the *p*-chlorobenzaldehyde-hydrogen peroxide adduct exhibits little or no curvature at formate buffer concentrations up to 1.8 *M*,[6] we undertook the experiments reported here in an attempt to characterize more completely the factors that can give rise to nonlinearity and other anomalies in buffer catalysis.

A nonlinear dependence of observed rates or experimental rate constants on buffer concentration at constant ionic strength may be caused by one or more of the following.

(1) A change in rate-determining step with increasing buffer concentration, from a step with a large ratio $k_{\text{buffer}}/k_{\text{solv}}$ at low buffer concentration (k_{solv} refers to the uncatalyzed reaction plus any catalysis by components of the solvent) to a step for which this ratio is smaller or zero at higher buffer concentration.[7,8] It is ordinarily not possible without further information to determine which step is rate determining in the high and low ranges of buffer concentration.[8]

(2) Self-association of the buffer to form complexes with reduced or no catalytic activity. For example, the formation of significant amounts of carboxylic acid and acid-anion dimers, $(RCOOH)_2$ and $(RCOOH{\cdot}OOCR)^-$, in concentrated buffer solutions has been claimed[9-14] and contested.[15,16] The formation of such dimers is of special interest to the extent that it can provide information regarding the strength of hydrogen bonding and "hydrophobic" interactions in aqueous solution. The self-association of borates is sufficient to interfere seriously with the study of catalysis by borate buffers.[17]

(3) Formation of a complex of a reactant and a component of the buffer that is caused by either covalent or noncovalent interactions.[8,18] Incorporation of a significant fraction of reactant or catalyst into the complex will ordinarily result in a downward curvature of rate against buffer concentration, regardless of whether or not the complex is itself reactive. If the complex is reactive, i.e., if the geometry of the complex is favorable for interaction of the reacting and catalyzing groups, the apparent catalytic constant at low buffer concentration may be larger than that for noncomplexing buffers of the same p*K*.[19]

(4) A specific salt effect will cause upward or downward deviations in plots of rate against buffer concentration if the buffer salt and the salt that is used to maintain constant ionic strength have different effects on the ratio of activity coefficients for the reactants and transition state. Such effects are particularly important in aqueous-organic solvent mixtures because of salt-induced medium effects (including "solvent sorting") and are likely to make the evaluation of catalytic constants difficult or impossible in such mixtures.[20,21]

(5) A nonspecific solvent effect caused by a component of concentrated buffer solutions can cause upward or downward deviations by affecting the same activity coefficient ratio. In addition, concentrated buffer solutions may affect the rate simply by decreasing the availability of water.

(6) Changes in pH with increasing buffer concentration when the baseline reaction is pH dependent. This is especially likely with buffers prepared from relatively strong acids or bases, which undergo a change in buffer composition with changing concentration unless strong acid or base is added to maintain constant pH. The measured pH may also vary because of changes in liquid junction potentials and other effects of salt and solvent on electrodes. Because of these medium effects, catalytic constants should generally be determined from the stoichiometric concentrations of added buffer components, which will ordinarily be very close to the true concentrations, and not from the total buffer concentration, the measured pH, and the pK of the buffer.

(7) Changes in the pK_a' of a reactant that give rise to changes in the concentration of the reactive form of the reactant with increasing buffer concentration. Such changes can sometimes be measured directly or evaluated from the effect of buffer on a reaction of the same reactant that is not subject to buffer catalysis. The effects of 3-7 on the baseline rate and on apparent pH or p*K* values can frequently be evaluated from measurements of the rate in the presence and absence of a component of the buffer at a pH value at which buffer catalysis is insignificant.

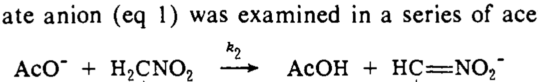
(8) A term in the rate law that is second order with respect to buffer concentration will give rise to an upward curvature with increasing buffer concentration. Terms of the form $k_{AB}[\text{reactant}][HA][A^-]$ mean that the elements of both the acidic and basic species of the buffer are incorporated into the transition state and have been referred to as concerted, third-order, ternary, second-order, bimolecular, acid-base, synchronous, push-pull, polyfunctional, and bifunctional catalysis.[22-28] We prefer the term bifunctional catalysis because it carries no implication with respect to the timing or the mechanism of proton transfer. Upward curvature could also be caused by the formation of a highly reactive $(AH{\cdot}A)^-$ complex with a low association constant; the high reactivity of such a complex would presumably arise from bifunctional catalysis.[22,25,29,30]

(9) Unrecognized effects of buffer on experimental or assay techniques used for rate measurements that cause errors in the determination of rate constants at high buffer concentrations.

We report here an examination of a series of buffer-catalyzed reactions, most of which are unlikely to undergo a change in rate-determining step, that illustrates several of these effects with special reference to the possible existence and importance of dimer formation in carboxylic acid buffers. The observed effects are indicated by number after the name of each reaction. It is concluded that dimer formation in acetate and formate buffers is insignificant under the conditions ordinarily used for kinetic measurements with these buffers, but that there is a small amount of downward curvature in concentrated formate buffers that can be accounted for by dimer formation.

Results and Discussion

(1) Acid Dissociation of Nitroethane (4, 9). The reaction of the carbon acid nitroethane with acetate ion to give the nitronate anion (eq 1) was examined in a series of acetate



$$\mathrm{AcO^- + \underset{\displaystyle CH_3}{\underset{|}{H_2CNO_2}} \xrightarrow{k_2} AcOH + \underset{\displaystyle CH_3}{\underset{|}{HC{=}NO_2^-}}} \qquad (1)$$

buffers to determine whether formation of an $[AcOH{\cdot}OAc]^-$ complex would lead to a nonlinear increase in rate at high buffer concentrations. This reaction was chosen because it is relatively simple and is unlikely to undergo a change in rate-determining step or to be subject to bifunctional acid-base catalysis by two molecules of buffer.

The observed pseudo-first-order rate constants show an *upward* curvature with increasing concentration of acetate buffer that is most noticeable with the 80% anion buffer, when the ionic strength is maintained constant at 2.0 *M* with potassium nitrate (Figure 1, open circles). The initial slopes of the plots against total buffer concentration (broken lines) are plotted against the percent of the buffer as the anion in the inset in Figure 1 to give the value of k_2 (eq 1) as the intercept at 100% AcO^-; the intercept at 0% AcO^- shows that acetic acid has no detectable activity as a catalyst. At first glance, the upward curvature might be taken as evidence for a term in the rate law involving bifunctional catalysis by a second molecule of buffer. However, bifunctional catalysis of the formation of the weakly basic nitroethane anion (the pK_a of *aci*-nitroethane[31] is 4.4) by acetic acid (pK_a = 4.7) is unlikely and, in any case, the apparent catalysis is most significant in the most basic buffer solution containing 80% acetate anion; i.e., it involves two molecules of the *basic* form of the buffer. In fact, the data may be described by the rate law of eq 2, with $k_2 = 2.5 \times 10^{-3}\ M^{-1}\ \text{min}^{-1}$ and $k_3 = 0.25 \times 10^{-3}\ M^{-2}\ \text{min}^{-1}$.

$$v = k_2[AcO^-][EtNO_2] + k_3[AcO^-][EtNO_2][RCOO^-] \quad (2)$$

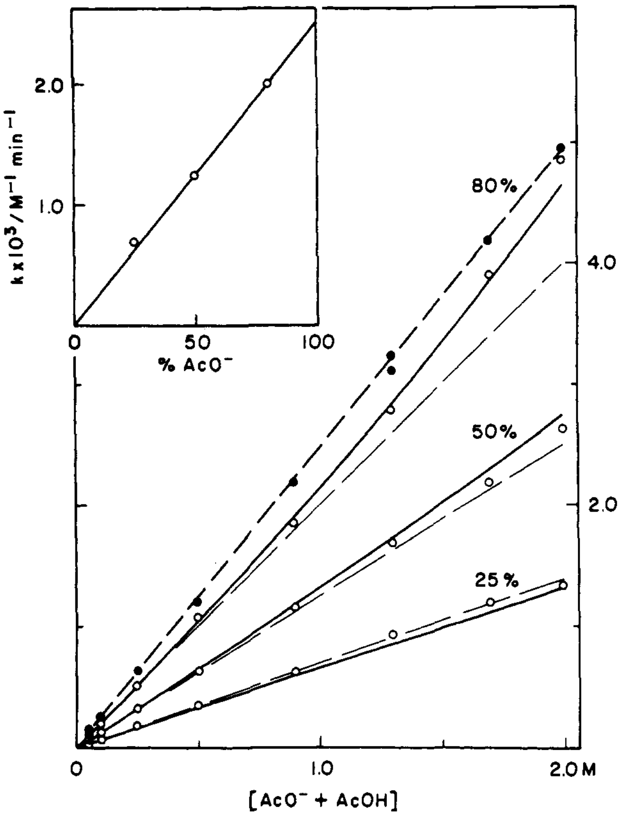


Figure 1. First-order rate constants for the ionization of nitroethane as a function of total acetate buffer concentration at 25, 50, and 80% AcO^- at 25°, 1.2% EtOH, and ionic strength 2.0 *M*: (○) ionic strength maintained with KNO_3; broken lines, initial slopes; solid lines, calculated *k* including specific salt effect (see text); (●) ionic strength maintained with F_3CCO_2K. Inset: initial slopes of KNO_3 experiments plotted as a function of percent AcO^-.

The upward curvature may be accounted for by a specific salt effect that causes a rate increase when nitrate anion is substituted by acetate anion as the buffer concentration is increased at constant ionic strength. This is shown by the fact that the rates are slightly faster and increase linearly with increasing buffer concentration when the ionic strength is maintained constant with potassium trifluoroacetate instead of potassium nitrate, as shown by the solid circles and upper dashed line in Figure 1. Trifluoroacetate resembles acetate more closely than does nitrate but is weakly basic and is not itself an effective catalyst. This is shown by the negligible intercept of the upper dashed line at zero buffer concentration, at which the concentration of trifluoroacetate ion is 2.0 *M*. Based on Brønsted β values of 0.5–0.65 for this reaction,[32] the value of k_2 for trifluoroacetate is expected to be some 200-fold smaller than that for acetate, in agreement with the absence of detectable catalysis. The salt effect is proportional to the concentration of $RCOO^-$ and can be described by the k_3 term of eq 2. The lines in Figure 1 are calculated from eq 2, based on values of $k_3 = 0.25 \times 10^{-3}\ M^{-2}\ \text{min}^{-1}$ for acetate ion and $0.30 \times 10^{-3}\ M^{-2}\ \text{min}^{-1}$ for trifluoroacetate ion, and show satisfactory agreement with the data.

The absence of downward curvature in the lines of Figure 1 demonstrates that there is no significant formation of a catalytically inactive $(AcOH{\cdot}OAc)^-$ complex at buffer concentrations up to 2.0 *M*, even in the presence of 1.5 *M* acetic acid. If a complex is formed, it must have the same catalytic effect as acetate ion so that it is not kinetically significant. Bell and McCoubrey have shown that the bifluoride ion, $[FHF]^-$, has no detectable activity as a base catalyst for enolization or nitramide decomposition.[33]

The rate of ionization of nitroethane was followed by trapping the nitroethane anion by reaction with iodine and measuring the disappearance of the absorbance of triiodide ion, which is in equilibrium with iodine in the presence of excess iodide ion (eq 3 and 4):

$$\frac{d[EtNO_2]}{dt} = \frac{dA/dt}{\text{fraction } I_3^- \ \epsilon_{I_3^-}} \quad (3)$$

$$I_2 + I^- \overset{K_{I_3^-}}{\rightleftharpoons} I_3^- \quad (4)$$

An upward curvature, which might be mistaken for a more than first-order dependence on buffer concentration, is also obtained if the zero-order slopes for the disappearance of the absorbance of triiodide ion are plotted against buffer concentration for experiments in which the ionic strength is maintained constant with potassium chloride (Figure 2, open circles). This can be accounted for by the complexation of chloride ion with iodine to form I_2Cl^- (eq 5):

$$I_2Cl^- \overset{K_{I_2Cl^-}}{\rightleftharpoons} I_2 + Cl^- \quad (5)$$

This complexation reduces the concentration and therefore the absorbance of triiodide ion in the runs containing the higher concentrations of chloride ion so that the total absorbance change for a given amount of iodine utilization is decreased in these runs.

The correct rates of iodine uptake and nitroethane disappearance may be obtained from eq 6, in which $[I_2]_{tot}$ is the total iodine concentration based on the amount of added iodine, including I_2, I_3^-, I_2Cl^-, and any other complexed species, and A_i and A_f refer to the initial and the final measured absorbance, respectively, in a given experiment. Equation 6 is based on eq 7, in which $\epsilon_{I_2}{}^*$ is an empirical extinction coefficient for $[I_2]_{tot}$ at 351 nm in a given experiment. First-order rate constants were obtained by dividing these rates by the nitroethane concentration and are plotted as closed circles in Figure 2; they exhibit a markedly decreased curvature. The residual curvature is presumably caused by a specific salt effect upon the substitution of acetate for chloride ion, analogous to that observed in the experiments with nitrate ion. The decrease in the concentration of I_3^- and in the observed absorbance changes at high chloride ion concentrations is consistent with the dissociation constant $K_{I_2Cl^-} = 0.6\ M$ estimated by Cason and Neumann under slightly different conditions.[34]

$$\frac{d[EtNO_2]}{dt} = \frac{d[I_2]_{tot}}{dt} = \frac{dA/dt}{\epsilon_{I_2}{}^*} = \frac{[I_2]_{tot}dA/dt}{A_i - A_f} \quad (6)$$

$$\epsilon_{I_2}{}^*[I_2]_{tot} = A_i - A_f \quad (7)$$

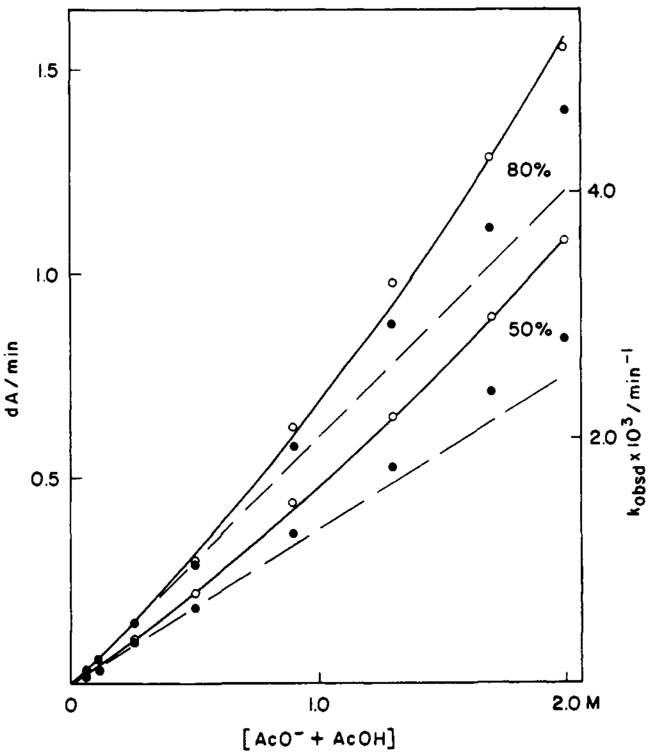


Figure 2. Ionization of nitroethane as a function of total acetate buffer concentration at 50% AcO^- (1.2 v% EtOH) and 80% AcO^- (0.6 v% EtOH) at 25° and ionic strength 2.0 *M* maintained with KCl: (○) change in absorbance/min of solutions containing 1.5×10^{-2} *M* nitroethane, 3.55×10^{-5} *M* I_2, and 0.01 *M* KI (left ordinate); (●) d*A*/min converted to first-order rate constants (see text); dashed lines, initial slopes (right ordinate).

(2) Protonation of Nitroethane Anion by Formic Acid (2, 6, 7). Formate buffers, in contrast to acetate buffers, give rise to a *downward* curvature of the rate with increasing concentration at constant ionic strength that can be accounted for by the formation of a catalytically inactive $(HCOOH{\cdot}OOCH)^-$ complex (Figure 3). Catalysis of the nitroethane reaction was studied in the direction of carbanion protonation by formic acid (eq 8, k_{-2}) because the direct reaction of formate ion with iodine (see below) interferes with measurements of nitroethane ionization by the iodine scavenger method.

$$\begin{tikzcd} CH_3CH{=}NO_2^- \arrow[r, shift left, "k_{-2}[HA]"] \arrow[d, shift left, "\pm H^+"] & CH_3CH_2NO_2 \arrow[l, shift left, "k_2[A^-]"] \\ \underset{aci\text{-}H}{CH_3CH{=}NO_2H} \arrow[u, shift left, "K_A"] & \end{tikzcd} \quad (8)$$

The catalyzed reaction follows the rate law of eq 9

$$v = k_{-2}[HCOOH][aci^-] = k'[HCOO^-][aci\text{-}H] \quad (9)$$

in which aci^- and *aci*-H refer to nitroethane anion and the O-protonated, aci form of nitroethane, respectively. The pK_a of *aci*-nitroethane was determined spectrophotometrically at 235 nm and was found to be 4.21 at ionic strength 2.0 *M* (KCl), 25°; this is slightly lower than the pK_a of 4.4 at ionic strength <0.01,[31] in accord with the difference in ionic strength. The initial slopes of the lines in Figure 3 divided by the fraction aci^- (based on $pK_a = 4.21$ and the observed pH at the lowest buffer concentration) are plotted in the inset as a function of the fraction of formate ion in the buffer and give an intercept of $k_{-2} = 43\ M^{-1}\ min^{-1}$ for the reaction with formic acid. The solid lines in the figure are calculated from the rate law of eq 9 and the free formic acid concentration, based on a value of $K_{12} = 0.25\ M^{-1}$ for formation of the $(HCOOH{\cdot}OOCH)^-$ complex (eq 10):

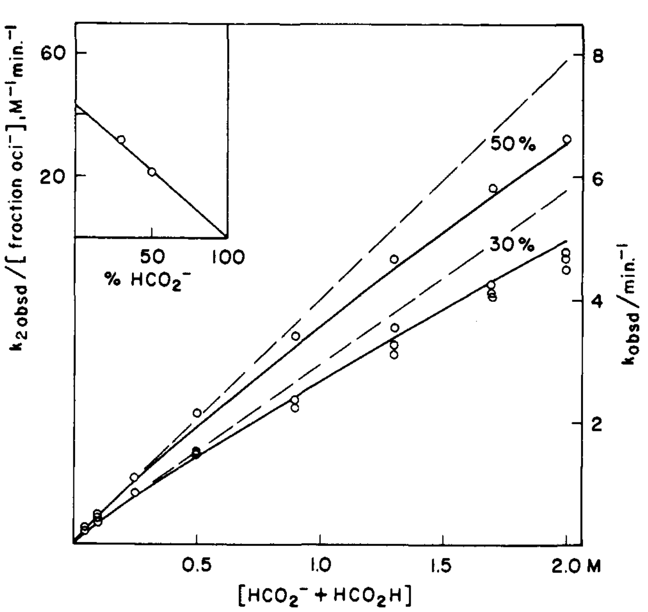


Figure 3. Observed pseudo-first-order rate constants for protonation of nitroethane anion at 25°, ionic strength 2.0 *M* (KCl) as a function of total formate buffer concentration at 30 and 50% HCO_2^-. The lines are calculated for $k_{-2} = 43\ M^{-1}\ min^{-1}$ and $K_{12} = 0.25\ M^{-1}$. Inset: initial slopes divided by fraction aci^-.

$$HCOOH + {}^-OOCH \overset{K_{12}}{\rightleftharpoons} HCOOH{\cdot}{}^-OOCH \quad (10)$$

The curvature in the plots is fit by this value of the association constant K_{12} within experimental error.

Curvature in plots of k_{obsd} against buffer concentration that might be mistakenly identified as evidence for buffer association can also be caused by (a) a change in pH with increasing buffer concentration due to specific salt or solvent effects that results in a change in the fraction of the substrate in the reactive ionic form at high buffer concentrations or (b) a change in the (concentration) dissociation constant of a reactant with increasing buffer concentration that leads to the same result. In fact, effects on both the pH and the dissociation constant of the reactant occur in the formic acid-*aci*-nitroethane system. A progressive change in the measured pH of up to 0.08 unit was observed as the concentration of formate buffer was increased from 0.05 to 2.0 *M*. However, the total absorbance change upon conversion of nitroethane anion to nitroethane was found to be constant with increasing buffer concentration, which demonstrates that the fraction of the aci form present as the anion is independent of buffer concentration. Evidently, the apparent pK_a values of formic acid and *aci*-nitroethane change in the same way with increasing buffer concentration so that no correction for these changes is required in this system. The structures of the reactants and products are similar for the two ionization processes, so it is not surprising that the activity coefficient terms for the two reactions should cancel. A similar result was found for the ionization of *aci*-nitroethane in 0.01 *M* acetate buffers (25% anion) and 2.0 *M* potassium chloride in the presence of added methanol. In the presence of 0, 1.0, and 2.0 *M* methanol, the fraction of *aci*-nitroethane anion, measured spectrophotometrically, was found to remain constant (0.494, 0.496, and 0.492, respectively), although the apparent pK_a values of acetic acid and *aci*-nitroethane increased by 0.2 unit.

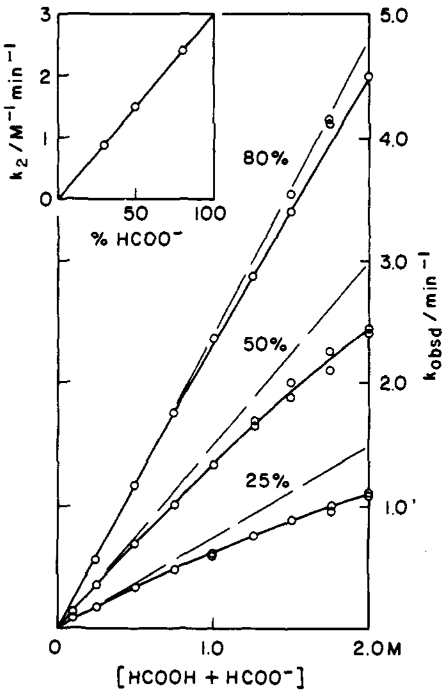


Figure 4. The reaction of iodine with formate buffers, 25, 50, and 80% $HCOO^-$, at 25° and ionic strength 2.0 *M* (KNO_3). The calculated, curved lines are based on values of k_a = 3.0 M^{-1} min^{-1} and K_{12} = 0.25 M^{-1}. The initial slopes of these lines are plotted in the inset against the percent formate ion in the buffer.

(3) The Reaction of Iodine with Formate Ion (2). The pseudo-first-order rate constants for the reaction of iodine with excess formate ion at ionic strength 2.0 *M* (eq 11)

$$I_2 + HCOO^- \xrightarrow{k_a} 2I^- + CO_2 + H^+ \qquad (11)$$

show a nonlinear dependence on the concentration of formate buffer that is most marked for buffers containing 50 and 75% formic acid (Figure 4). The downward curvature is consistent with a decrease in the concentration of free formate ion caused by the formation of an unreactive $[HCOOH{\cdot}OOCH]^-$ complex in the presence of formic acid. The curves in Figure 4 are drawn based on a second-order rate constant k_a = 3.0 M^{-1} min^{-1} (eq 12) and an association constant for complex formation K_{12} = 0.25 M^{-1}.

$$v = k_a[I_2][HCOO^-] \qquad (12)$$

The calculated lines provide a satisfactory fit to the data. The value of k_a was obtained from a plot of the initial slopes of the lines in Figure 4 against the percent $HCOO^-$ in the buffer (see inset). Values of k_a in the range 1.2-1.3 M^{-1} min^{-1} have been reported previously at ionic strength 0-0.1 *M*.[35,36]

The nonlinearity does not appear to be caused by a specific salt effect nor by a nonspecific solvent effect from the addition of formic acid. An identical rate constant was obtained when the ionic strength was maintained with potassium trifluoroacetate instead of potassium nitrate in the presence of 1.0 *M* formic acid buffer, 50% acid. The addition of 2.0 *M* ethanol or methanol was found to have no effect on the rate, and 2.0 *M* acetonitrile causes a 20% *increase* in the observed rate.

Several other possible causes of nonlinearity with respect to buffer concentration are excluded by the observation that the observed change in absorbance from the disappearance of I_3^- shows only a random variation (≤4%) and no dependence on buffer concentration in a series of runs (in order to achieve a constant absorbance change, it was necessary to avoid smoking before pipetting; tobacco smoke causes a decrease in initial absorbance). The consumption of iodine was followed spectrophotometrically in the presence of a large excess of iodide ion by measuring the disappearance of the absorbance of I_3^-, which is in equilibrium with free iodine (eq 4). A nonlinear dependence on buffer concentration could be caused by (a) a salt or solvent effect on the equilibrium constant $K_{I_3^-}$ that would change the amount of free iodine that is available for reaction at high buffer concentrations, (b) formation of an inactive complex between iodine and formic acid, or (c) accumulation of an intermediate, such as HCOOI, that would decrease the concentration of free iodine and lead to a leveling off of the rate. The constancy of the observed changes in absorbance and the absence of a rate decrease in the presence of 2 *M* organic solvents or upon substitution of trifluoroacetate ion for nitrate ion provide evidence against a significant decrease in the concentration of free iodine from effects of this kind. In order to account for the observed 25% rate decrease in 2.0 *M* formate buffer, 25% anion, the concentration of iodine would have to be reduced by 25%; such a decrease would require an increase in $K_{I_3^-}$ from 630 to 1000 M^{-1}.

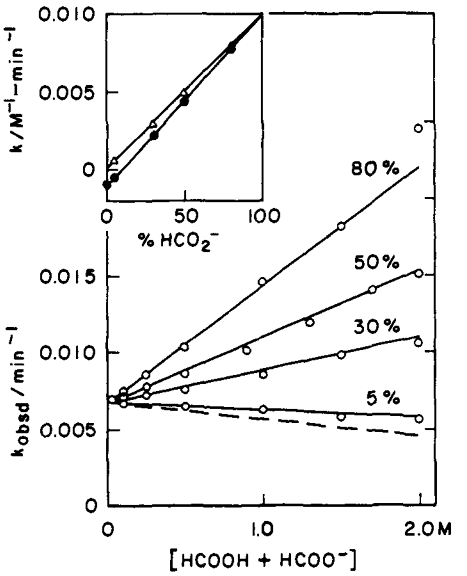
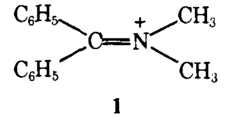


Figure 5. Catalysis by formate buffers of the hydrolysis of benzhydrylidenedimethylammonium ion at 25° in aqueous 1.3% acetonitrile and ionic strength 2.0 *M* maintained with KCl. First-order rate constants (○) as a function of total buffer concentration (5, 30, 50, and 80% HCO_2^-). Dashed line: calculated first-order rate constants at 0% HCO_2^-. Inset: observed second-order rate constants for buffer catalysis (●) as a function of % HCO_2^-; (Δ) same, after correction for $k_4(H_2O)^4$.

The reaction involves a direct attack of iodine on formate ion, presumably involving the transfer of hydride ion;[36,37] an alternative mechanism involving the intermediate formation of HCOOI is inconsistent with the isotope effect for deuterioformate ion of k_H/k_D = 3.8 and with the inverse first-order dependence of the observed rate on the concentration of I^- in the presence of I_3^-. Hydrogen bonding of formate ion to formic acid in the complex is expected to inhibit the donation of electrons from oxygen that is required for transfer of the hydride ion.

(4) Hydrolysis of Benzhydrylidenedimethylammonium Ion (BDA^+) (5). Catalysis of the hydrolysis of this cationic imine (**1**) by formate buffers is linear with respect to buffer concentration, within experimental error, up to buffer concentrations of 2.0 *M* (Figure 5). This catalysis is kinetically un-



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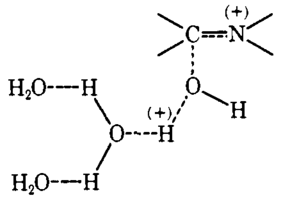
ambiguous and represents the removal of a proton by formate ion from the attacking water molecule.[38] Although the curves at each buffer ratio are linear, the experiment with a 5% formate–95% formic acid buffer shows a small inhibition rather than catalysis with increasing buffer concentration, and a plot of the observed catalytic constants for each buffer ratio against the fraction of formate ion in the buffer exhibits a negative intercept on the ordinate corresponding to "negative catalysis" by pure formic acid, as shown by the lower line in the inset. Correction of the observed rate constants from runs in 5% formate anion buffers for catalysis by formate anion, based on the catalytic constant for formate anion of 0.01 M^{-1} min^{-1} (see inset), gives the dashed line in the figure showing the inhibition by formic acid. The slope of this line (a "rate constant for negative catalysis") is -0.001 M^{-1} min^{-1}, which is included as the lowest point in the inset.

The inhibition by formic acid does not represent negative catalysis resulting from an increased rate of return of an intermediate to starting materials in the presence of formic acid, because such catalysis violates the principle of microscopic reversibility. If a certain amount of a catalyst in a given solution lowers the free energy of activation for a reaction in one direction by a certain amount, it must lower it by the same amount in the opposite direction under the same conditions (so long as there is no change in equilibrium constants, i.e., when the catalyst is a true catalyst) so that inhibition of a reaction by catalysis in one direction is not possible. A decrease in rate caused by formic acid cannot be explained by a change in rate-determining step; in any case, the common intercepts at zero buffer concentration indicate that there is no change in rate-determining step in the pH region examined.

The rate decrease can be explained simply by the decrease in water concentration in the presence of formic acid if it is assumed that a total of four water molecules are required for the reaction. The addition of water to BDA$^+$ generates a proton and, if it is assumed that this proton is solvated by three water molecules in addition to the attacking water molecule, as in the case of $H_9O_4^+$, **2** represents a plausible structure for the transition state. The observed general base catalysis by buffer bases suggests that proton transfer is necessary for the formation of a relatively stable transition state that goes on to products. The rate constant for the water reaction ($k_{obsd}/55$) falls near the Brφnsted line of slope $\beta = 0.27$ for more basic catalysts reported by Koehler et al.,[38] suggesting that the water reaction also involves proton transfer. A plot of log k for the hydrolysis in the presence of formic acid against log $[H_2O]$ was found to have a slope of 4.0, consistent with the involvement of four water molecules in the transition state, and the observed inhibition is satisfactorily accounted for (dashed line, Figure 5) by the rate law of eq 13



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$$v = k_4[>C{=}\overset{+}{N}<][H_2O]^4 \qquad (13)$$

with $k_4 = 1.23 \times 10^{-9}$ M^{-4} min^{-1}. The observed rate constants were corrected for the water reaction according to eq 13 and corrected slopes of the plots of $k_{obsd} - k_4[H_2O]^4$ against buffer concentration are plotted as triangles in the inset of Figure 5. The corrected data show that the buffer catalyzed reaction is indeed proportional to formate ion and no other effects need be invoked to account for the data. While the data certainly do not establish that 4.0 water molecules are involved in the reaction, they are consistent with the hypothesis that several water molecules are involved in the proton abstraction by water and water attack. Addition of 2 M acetic acid (pH 1.82) was found to have no effect on the rate, and 2 M methanol and acetonitrile give rate increases of 18 and 40%, respectively. Evidently these organic solvents cause a positive solvent effect on the rate that is sufficient to overcome any unfavorable effect of decreasing water concentration.

It should be noted that only the water reaction is significantly inhibited by formic acid; there is no detectable downward curvature in the plots that would be expected if formic acid caused significant inhibition of the formate-catalyzed hydrolysis (for example, 10% inhibition at 1 M and 20% inhibition at 2 M buffer would give a significant downward curvature of the lines in Figure 5). This is consistent with the suggested explanation for formic acid inhibition since only one water molecule is required for the formate-catalyzed reaction.

The data provide no evidence for downward curvature caused by the formation of an unreactive [HCOOH·OOCH]$^-$ complex, but the amount of curvature that would be introduced by a value of $K_{12} = 0.25$ M^{-1} is less than the experimental uncertainty of the data because of the large contribution of the buffer-independent reaction to the observed rate. However, the absence of detectable curvature serves to exclude the formation of an unreactive complex with an association constant appreciably larger than 0.25 M^{-1}. The same conclusion applies to the dissociation of the p-chlorobenzaldehyde–hydrogen peroxide adduct in the presence of formate buffers, 65% anion.[6] Although the observed rate constants for this reaction appear to increase linearly with increasing buffer concentration up to 1.8 M, the data may also be fit satisfactorily with a calculated line based on the formation of an inactive dimer with $K_{12} = 0.25$ M^{-1}.

(5) Enolization of Cyclohexanone (5, 8). The rates of cyclohexanone enolization, measured by the iodine scavenger method in acetate buffers, 50% anion, exhibit an upward curvature with increasing buffer concentration that indicates a more than first-order dependence of the rate on buffer concentration (Figure 6). Similar, but less marked, curvature was observed with buffers containing 25 and 80% acetate ion. Very similar behavior was observed when the ionic strength was maintained at 2.0 M with potassium nitrate or with potassium trifluoroacetate, shown by the open and closed circles, respectively, in Figure 6, suggesting that the curvature does not represent a specific salt effect.

The data may be described by the rate law of eq 14.[22-26]

$$\frac{v}{[\text{ketone}]} = k_{H_2O} + k_{H^+}a_{H^+} + k_A[\text{AcOH}] + k_B[\text{AcO}^-] + k_{AB}[\text{AcO}^-][\text{AcOH}] \qquad (14)$$

The results were converted to rate constants according to eq 15.

$$k_{obsd} = \frac{dA/dt[I_2]_{tot}}{(A_i - A_f)[\text{ketone}]} \qquad (15)$$

The buffer-independent terms, k_{H_2O} and k_{H^+}, were evaluated by plotting the intercepts at zero buffer concentration against a_{H^+}, as shown by the solid circles in Figure 7. The observed rate constants were then corrected for the buffer-independent terms, divided by the concentration of acetate ion, and plotted against the concentration of acetic acid[24]

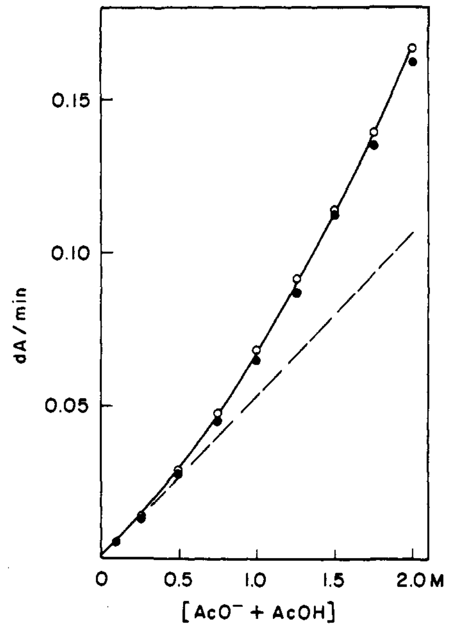


Figure 6. The dependence of the rate of enolization of cyclohexanone on the concentration of acetate buffer, 50% AcO^- at ionic strength 2.0 M and 25°. The ionic strength was maintained with potassium nitrate (○) or potassium trifluoroacetate (●). The dashed line shows the rate without bifunctional catalysis (from $k_{solv} + k_A + k_B$), and the solid line is calculated from eq 14 and 15 and the rate constants in Table I.

Table I. Rate Constants for the Enolization of Cyclohexanone and Acetone in Acetate Buffers at 25°

	Cyclohexanone[a]	Acetone[b]
$k_{H_2O} \times 10^8/\text{min}^{-1}$	33[d]	2.8
$k_{H^+} \times 10^3/M^{-1}\ \text{min}^{-1}$	10.2,[d] 13.8[c]	1.6
$k_A \times 10^5/M^{-1}\ \text{min}^{-1}$	1.4, 1.5[c]	0.5
$k_B \times 10^5/M^{-1}\ \text{min}^{-1}$	2.57, 2.35[c]	1.5
$k_{AB} \times 10^5/M^{-2}\ \text{min}^{-1}$	2.8	2.0

[a] This work, ionic strength 2.0 M (KNO_3). [b] Reference 29, ionic strength 0.2 M. [c] Reference 39, ionic strength 0.25 M. [d] Determined by A. F. Hegarty from experiments at low buffer concentrations. Less accurate values obtained in this study with higher buffer concentrations were used to correct for buffer-independent terms; closely similar values of k_A and k_B were obtained in the two studies.

(solid lines, Figure 8). The intercepts of these plots are equal to $k_B + k_A[AcOH]/[AcO^-]$, and the slopes are equal to k_{AB}. A plot of the intercepts against a_{H^+} gives k_B at $a_{H^+} = 0$ and k_A/K_{AcOH} as the slope (open circles, Figure 7).

The upward curvature of the line in Figure 6 and the positive slopes of the lines in Figure 8 establish the existence of a significant third-order term, k_{AB}, for the enolization of cyclohexanone, but the slopes of the solid lines in Figure 8 are not constant. This variation in slopes is attributed to a nonspecific solvent effect caused by the acetic acid in the concentrated buffer solutions because added acetonitrile and ethanol were found to *increase* the acetate-catalyzed reaction, measured in 1 M buffer, 80% AcO^-, and to *decrease* the acetic acid catalyzed reaction, measured in 1 M buffer, 10% AcO^-. A concentration of 5% (v/v) acetonitrile was estimated to increase k_B by 12% and to decrease k_A by 8%. Correction of the observed rate constants for this solvent effect, assuming that acetic acid and acetonitrile have equivalent effects, gives the dashed lines in Figure 8. Since the corrected lines are parallel to each other, a solvent effect can adequately account for the variation in k_{AB} obtained from the slopes of the solid lines.

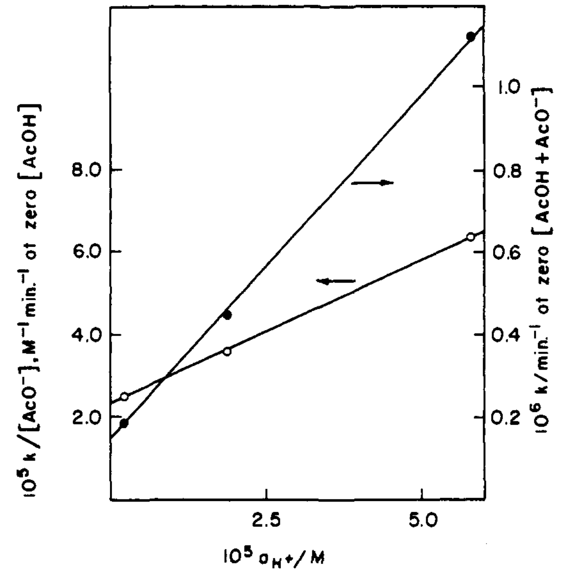


Figure 7. Buffer-independent rate constants for cyclohexanone enolization as a function of a_{H^+}. (●) right ordinate. Intercepts of Figure 8 as a function of a_{H^+}, (○) left ordinate.

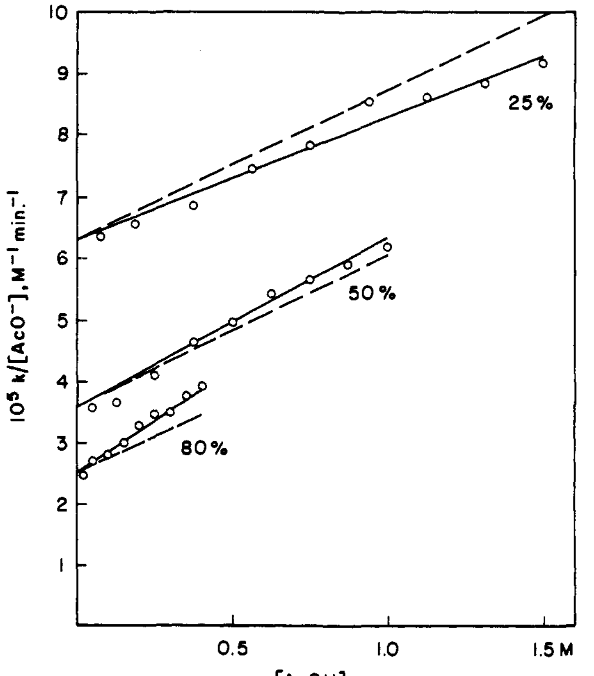
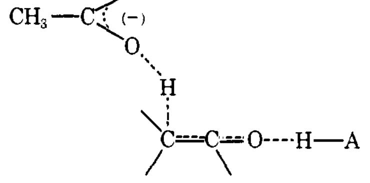


Figure 8. Solid lines: buffer-dependent rate constants for cyclohexanone enolization divided by acetate ion concentration as a function of acetic acid concentration. Dashed lines: same, but corrected for solvent effects on k_A and k_B.

The rate constants at ionic strength 2.0 M (KNO_3) are summarized in Table I together with previously reported values[39] obtained at ionic strength 0.25 M ($NaClO_4$) and lower buffer concentrations, at which the k_{AB} term was not detected. The rate constants for cyclohexanone are slightly larger than those for the enolization of acetone,[29] shown in the last column of Table I, and show the same order for the buffer terms.

The results confirm the existence of a significant third-order term for bifunctional acid-base catalysis of the enolization of ketones and provide evidence that this term is not an artifact resulting from a solvent or specific salt effect. There is no evidence for the formation of an $[AcOH{\cdot}OAc]^-$ complex at high buffer concentrations. It does not seem likely that the complex is itself the reactive species that accounts for the third-order term because this term is larger than either k_A or k_B, although hydrogen bonding is expected to reduce the basicity of the carboxylate group and the acidity of the proton.[22,25,29,30] It would be surprising if the four-atom, nonlinear hydrogen bond that is required for a cyclic, bufunctional mechanism of catalysis[25] could provide significant extra stabilization to the transition state in view of the known instability of hydrogen-bonded complexes in water, and it has been reported that ketonization of the dianion of oxaloacetic acid exhibits a significant third-order term for catalysis by imidazole, which cannot form such a cyclic transition state.[26] Furthermore, a number of dicarboxylic acid monoanions that might be expected to provide effective bifunctional catalysis are not especially effective catalysts for the enolization of acetone in water,[40] and hydrogen bonded complexes of acetic acid are inactive as acid catalysts for oxazolin-5-one ring opening in carbon tetrachloride.[41]

The rate constants for general acid catalysis by acetic acid and water of the acetate-mediated enolization (**3**) correspond to Brϕnsted α values of 0.16 for both cyclohexanone and acetone. The water reaction cannot represent concerted proton transfer from water to the developing oxyanion, because there is no thermodynamic advantage to be gained from such concerted catalysis.[28,42] This low α value is consistent with transition state **3**, in which the role of the acid catalyst is to stabilize the developing negative charge on oxygen by hydrogen bonding. In any case, an upper limit of $\alpha \sim 0.5$ is set for general acid catalysis by carboxylic acids of acetate-mediated enolization by the rate constants k_{AB} and k_A. It has been demonstrated by the use of enol ethers as models for the reverse, ketonization reaction and from isotope effects that the k_A term represents *specific* acid catalysis by the solvated proton of the acetate-mediated enolization, $k_A'[H^+][AcO^-][\text{ketone}]$, so that the rate constant for *general* acid catalysis by the solvated proton must be less than the observed k_A' term.[25,39,43]



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The Brϕnsted β value of 0.88 for acetone enolization[44] implies a late transition state with a large amount of negative charge development on the carbonyl oxygen atom, and the existence of bifunctional, third-order catalysis in this reaction may be reasonably attributed to stabilization of this negative charge by acetic acid.

Acid-Carboxylate Complexes. The published evidence is contradictory with respect to the properties, and even the existence, of hydrogen-bonded complexes between carboxylic acids and carboxylate ions in aqueous solution. Formation constants on the order of 0.1 M^{-1} have been reported for $(AcOH{\cdot}OAc)^-$ and $(AcOH)_2$ dimers and similar values, as well as a number of physical properties, have been reported for a number of dimeric species of this kind, based on potentiometric, cryoscopic, vapor pressure, and distribution measurements and on Raman spectroscopy.[9-14] However, most of these techniques (with the exception of the examination of $(AcOH)_2$ formation by Raman spectroscopy[11]) are basically methods for measuring the activity of the various solute species. Since changes in activity can result from changes in activity coefficients in the relatively concentrated solutions of salts and acids that are generally examined by these techniques, as well as from dimer formation, it is difficult to determine the association constants, or even the existence, of dimeric species with certainty. In addition, the potentiometric technique presents special problems that arise from changes in liquid junction potentials and other effects of solvent on the measurement technique. In fact, Persson has found that potentiometric measurements give different dimer formation constants with hydrogen and with glass electrodes and no evidence for dimer formation with cadmium amalgam electrodes. He has concluded that pH measurements in acetic acid-acetate solutions are influenced more by changes in activity factors and liquid junction potentials than by hypothetical dimeric acetate species, and that the formation of proton acetate dimers in water solution is very questionable; if such species exist at all, they are formed to a negligible extent.[16]

The data reported here do not reveal any kinetically significant formation of dimeric species in acetate buffers, in agreement with this conclusion. The results with formate buffers, on the other hand, suggest significant formation of a $(HCOOH{\cdot}OOCH)^-$ complex that can be described by an association constant $K_{12} = 0.25\ M^{-1}$. Most of the reported association constants for formic acid dimerization are small, in the range 0.01 to 0.1 M^{-1}, but the reported values of K_{12} for formation of the acid-anion complex are in the range 0.32 to 0.48 M^{-1} in the presence of 3 M sodium chloride or potassium chloride, or 5 M sodium perchlorate.[9,12-14] Although these values are based on potentiometric measurements and are subject to the same uncertainties as those for the acetic acid system, the fact that the values of K_{12} for $(HCOOH{\cdot}OOCH)^-$ formation are significantly larger than the reported value of $\sim 0.1\ M^{-1}$ for the corresponding acetic acid complex[10] provides support for the formation of a significant amount of the formate complex and is probably consistent with the value of $K_{12} = 0.25\ M^{-1}$ obtained from our kinetic measurements at ionic strength 2.0 M.

Association constants of this magnitude require careful definition and examination with respect to the particular experimental property and technique that is utilized for their determination.[45,46] Equilibrium constants that describe the formation of random encounter complexes between two molecules A and B in aqueous solution are in the range 0.017 to 0.3 M^{-1}, depending on the steric requirements, number of nearest neighbors, and intermolecular distance required for the formation of a particular complex.[45,47] The formation of such a complex implies no preferential interaction of A with B relative to solvent molecules. Such complexes will affect properties of A that require only that B be within a certain distance of A, such as charge transfer absorption, other spectroscopic properties, the rates of diffusion-controlled reactions, and the activity of A as a catalyst for reactions of B through a preassociation or "spectator" mechanism.[48] When molecules within the complex interact with each other in essentially the same way as with the solvent, the tendency of a complexed molecule to ionize, react with another molecule outside the complex, or act as a catalyst should be essentially the same as for a monomeric molecule that is surrounded by solvent. Therefore, the formation of a random encounter complex between two molecules of a buffer, such as $RCOO^-$ and RCOOH, should not give rise to a nonlinear dependence of rate on buffer concentration in the absence of solvent effects.

On the other hand, if there is a favorable interaction between A and B that is significantly stronger than the interaction with solvent, through hydrogen bonding for example, this preferential interaction will lead to complex formation that is in excess of that expected from random encounters and is likely to alter the chemical reactivity of the complexed molecule. Formation of this kind of "sociation complex"[49] between buffer molecules will result in a nonlinear dependence of rate on the concentration of buffer. When the rate of reaction of the complexed species is negligible, the equilibrium constant for formation of the sociation complex may be obtained from Benesi-Hildebrand and related reciprocal plots.[45] When this equilibrium constant is small, it does not provide a direct measure of the number of molecules in contact with each other because a comparable or even larger number of molecules will be in contact in random encounter complexes.

Complex formation that does not involve or change the properties of the reacting groups will not give rise to nonlinear dependence on reactant concentration for ordinary chemical reactions, and complexes with a reduced but significant reactivity will give intermediate behavior. For example, the reactivity of the carboxylate group of a hypothetical ($HOOCCH_3 \cdot CH_3COO^-$) complex held together by a hydrophobic interaction between the methyl groups[12] would presumably be similar to or identical with that of free acetate. On the other hand, a system in which increasing the number of molecules of B in the solvation shell of A from one to two does not double the probability of reaction *will* give nonlinearity with respect to the concentration of B from encounter complex formation, in the absence of any preferential interaction or sociation complex formation. This will be the case when a reaction or spectral manifestation can occur at more than one solvation site around A and is proportional to the occupancy of *any* such site by B, as in a diffusion-controlled reaction or charge transfer absorption with little or no orientation requirement for example.

The association constant $K_{12} = 0.25\ M^{-1}$ for the formation of $(HCOOH \cdot OOCH)^-$ and comparable equilibrium constants for other systems are defined empirically; they are useful because they provide a satisfactory description of the experimental data. The determination of K_{12} assumes that the $(HCOOH \cdot OOCH)^-$ complex is catalytically inactive, and this assumption is consistent with the data. However, it must be recognized that this equilibrium constant does not provide a direct measure of the number of $(HCOOH \cdot OOCH)^-$ dimers in the solution, of the number of such dimers that are hydrogen bonded, nor of the reactivity of the complexed or hydrogen bonded molecules. A significant number of formate ions will exist in random encounter complexes with formic acid, and at least some of these complexes will be hydrogen bonded. In fact, the data for the formate-iodine reaction (Figure 4) can be fit satisfactorily with association constants as large as $K = 1.0\ M^{-1}$, if it is assumed that the complex is reactive with a specific rate constant of $1.5\ M^{-1}\ \mathrm{min}^{-1}$; larger values of K give curves with a different shape from that observed. It is not unlikely that dimeric complexes will be found to exhibit significant catalytic activity in a number of reactions, especially in reactions with a low Brønsted α or β coefficient that require only the presence of a group that can donate or accept a proton in a multistep reaction mechanism.[28,48,50]

Further insight can be obtained from chemical information and the properties of stronger complexes, especially the bifluoride ion, FHF^-. The equilibrium constant of $4.0\ M^{-1}$ for the formation of this species requires that the hydrogen bond between F^- and HF be significantly more stable than a hydrogen bond with water. The findings that FHF^- has no detectable activity as a base catalyst for enolization or nitramide decomposition and no detectable activity as an acid catalyst for the protonation of enol ethers indicates that this hydrogen bond also serves to decrease the reactivity of both species in the complex, as would be expected on chemical grounds.[33,51] The action of FHF^- as an acid catalyst gives two fluoride ions as the immediate product and requires that the reverse reaction involve two molecules of base to abstract one proton;[33] such reactions that are second order with respect to base catalysts have not been described to our knowledge. A similar argument applies to base catalysis by FHF^-, which would require the donation of one proton from two HF molecules in the reverse direction. Furthermore, the proton in a hydrogen-bonded complex is tied up between two bases so that it is not readily available for reaction and it is known that the abstraction of a proton from between two basic groups in an internally hydrogen bonded system, such as a dicarboxylic acid monoanion, is several orders of magnitude slower than for other acids of comparable pK_a.[52] This suggests that the hydrogen bonded $(HCOOH \cdot OOCH)^-$ anion is not likely to be an effective acid catalyst for the protonation of nitroethane anion. The acidity of this species must be low because the conjugate base, a complex of two formate ions, is so unstable that it has not been detected.

For these reasons, because the same equilibrium constant fits the data for both the neutralization of nitroethane anion and the iodine-formate reaction, and because the data for the hydrolysis of BDA^+ and the dissociation of the *p*-chlorobenzaldehyde-hydrogen peroxide adduct[6] provide no evidence for a larger association constant, it appears reasonable to describe the behavior of the formate buffer systems in terms of the formation of a catalytically inactive hydrogen-bonded complex with a value of $K_{12} = 0.25\ M^{-1}$. For the same reasons, it is unlikely that the absence of detectable downward curvature in the plots for the deprotonation of nitroethane and cyclohexanone in acetate buffers could be accounted for by the formation of a dimeric species with a significant "sociation constant" and a catalytic activity equal to or greater than that of acetate ion. However, in both cases, it is certain that catalytically active dimeric species do exist in random encounter complexes, and the possibility of larger association constants for the formation of weak complexes with a significant catalytic activity cannot be rigorously excluded.

Experimental Section

Ionization of Nitroethane. Nitroethane was washed three times with 2.5% sodium bisulfite, three times with water, and once with saturated sodium chloride solution. After drying over calcium chloride, it was fractionally distilled, bp 114.8–115°. Stock solutions were prepared in ethanol and added to reaction mixtures to give a final concentration of 0.018 M nitroethane and 1.2% ethanol. The reaction was followed spectrophotometrically[53] by measuring the zero-order disappearance of I_3^- absorption at 351 nm in solutions that generally contained 0.01 M potassium iodide and 3 to $5 \times 10^{-5}\ M$ iodine. The total absorbance change was found to be constant in a series of runs when the ionic strength was maintained at 2.0 M with potassium nitrate or potassium trifluoroacetate. Zero-order rates were obtained from eq 3 or 6 and were divided by the concentration of nitroethane to obtain pseudo-first-order rate constants. The value of $\epsilon_{I_3^-}$ was found to be 25,500 $M^{-1}\ \mathrm{cm}^{-1}$, and the association constant $K_{I_3^-}$ (eq 4) was found to be 630 M^{-1} at ionic strength 2.0 M, maintained with potassium nitrate, from measurements of triiodide absorption in the presence of a constant amount of added iodine and 0.001 to 0.115 M potassium iodide; values of $\epsilon_{I_3^-} = 26{,}000\ M^{-1}\ \mathrm{cm}^{-1}$ and $K_{I_3^-} = 670\ M^{-1}$ have been reported in 0.2 M buffers.[54]

Protonation of *aci*-Nitroethane. The reaction was followed spectrophotometrically by measuring the pseudo-first-order disappearance of the absorption of *aci*-nitroethane anion at 250 nm. Stock solutions were prepared by incubating 0.266 mmol of nitroethane in 0.92 ml of water containing 0.246 mmol of potassium hydroxide for 25 min followed by dilution to 2.0 or 5.0 ml. Aliquots of the stock solution were added to reaction mixtures to initiate the reaction and give a final concentration of anion in the range 2.7×10^{-4} to $1.7 \times 10^{-3}\ M$. The fraction of *aci*-nitroethane present as the anion at different pH values was determined from the observed absorbance at 235 nm, extrapolated to zero time, of aliquots of the stock solution diluted into 0.01 M acetate buffers.

Oxidation of Formate by Iodine. The reaction was followed by measuring the pseudo-first-order disappearance of I_3^- absorbance in the presence of a large excess of formate buffer under the conditions described above, except that the final concentration of ethanol was 0.25%. Pseudo-first-order rate constants were obtained from linear plots of log $(A - A_\infty)$ against time and were divided by the fraction of free iodine (0.138) to obtain k_{obsd}.

Hydrolysis of Benzhydrylidenedimethylammonium Ion (BDA^+). This cationic imine[55] was kindly provided by Susan Moore. Reactions were initiated by the addition of 0.04 ml of a stock solution of ~3 mg BDA^+I^- in 1.0 ml of dry acetonitrile to 2.96 ml of formate buffer, ionic strength maintained at 2.0 M with potassium chloride, and were followed by measuring the change in absorption at 300 nm. The concentrations of water in solutions of 2 M HCOOH, 2 M KCl, and 2 M HCOOH + 2 M KCl were estimated gravimetrically to be 51.2, 52.5, and 48.2 M, respectively. The change in water concentration on replacement of KCl by HCOOK was neglected; this may introduce a small systematic error in the rate constant for formate catalysis but does not affect the calculations for inhibition by formic acid.

Enolization of Cyclohexanone. Cyclohexanone was fractionally distilled under argon, bp 154.5–155.5°, and stored under argon. The reaction was followed by measuring the zero-order disappearance of triiodide absorption,[39,56] as described above, after the addition of a freshly prepared stock solution of cyclohexanone in 60% acetonitrile to give a final concentration of 0.113 M cyclohexanone and 3.3% acetonitrile. The total absorbance change was found to be constant within a series of runs. The rate constants were not changed by doubling the concentration of cyclohexanone or incubating cyclohexanone with buffer prior to the addition of $KI-I_2$. Some experiments were carried out with a stored cyclohexanone preparation that caused an initial increase in triiodide absorption, presumably because of the presence of a contaminating peroxide, but the observed rate constants were found to be the same as those obtained with freshly distilled cyclohexanone. The value of a_{H^+} (eq 14) was assumed to be equal to antilog (− pH).

References and Notes

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