Nickel(II)-Catalyzed and Acid-Catalyzed Acetohydroxamic Acid Formation from Acetic Acid

James W. Munson and Kenneth A. Connors*

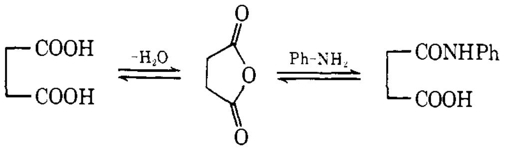
Contribution from the School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706. *Received July 30, 1971*

Abstract: Acetic acid and hydroxylamine form acetohydroxamic acid in aqueous solution in a reaction whose rate equation contains terms of the form $k[\mathrm{CH_3COOH}][\mathrm{NH_2OH}][\mathrm{H^+}]^n$, where n can be 0, 1, and 2. This reaction was studied at 90.5° over the pH range 0.54–5.68. Decomposition of a tetrahedral intermediate was postulated to be the rate-determining step. The kinetics of the reverse reaction, hydrolysis of acetohydroxamic acid, and the equilibrium constant for the reaction were also studied at this temperature. Under comparable conditions the catalysis of acetohydroxamic acid formation by nickel(II), first reported by Lawlor, was studied kinetically. This catalysis is thought to occur through a complex of Ni(II) with acetate ion, rendering the acetate more susceptible to nucleophilic attack by hydroxylamine. The form of the pH-rate profile in the Ni(II)-catalyzed system depends upon the ratio of hydroxylamine to Ni(II); this dependence is ascribed to different distributions of nickel–hydroxylamine complexes. The direct observation of hydroxamic acid formation in acid- and Ni(II)-catalyzed reactions appears to be ascribable to unusually high reactivity of hydroxylamine in these reactions rather than to any special characteristics of the acid substrates.

Amide formation from amines and carboxylic acids in aqueous solution may be one of the fundamentally important organic reactions. This reaction could have occurred in the primeval broth, which contained the necessary reactant molecules.[1] Although "activation" of an acyl group (as by converting it to an ester, acid anhydride, thiol ester, acyl phosphate, etc.) is usually considered to be prerequisite to amide formation, the free carboxylic acid should itself be a reasonable reactant, since the hydroxide ion will be about as good a leaving group as an alkoxide ion.[2] Morawetz and Otaki,[3] working with aliphatic carboxylic acids and aliphatic amines, were able to detect amide formation in aqueous solution. They wrote the rate equation for amide formation as $v = k[\mathrm{RCOO^-}][\mathrm{R'NH_2}]$, with typical values of the rate constant being of the order 10^{-8} $M^{-1}\ \mathrm{sec}^{-1}$ at 75° and the equilibrium constant of the reaction, when formulated according to eq 1, being 10^{-6} to 10^{-4} at 75°.[4]

$$\mathrm{RCOO^- + R'NH_2 \rightleftharpoons RCONHR' + OH^-} \qquad (1)$$

Higuchi and his coworkers have studied reversible amide formation between amines and dicarboxylic and tricarboxylic acids in aqueous solution.[5] The key experimental factor in these studies was the use of aromatic amines, whose pK_a values are low enough so that the unprotonated amine can coexist in significant concentrations with the undissociated acids. The intermediate formation of a cyclic anhydride was postulated, as shown for the succinic acid–aniline system in eq 2.



(2)

A rather special type of amide, a hydroxamic acid RCONHOH, can be formed by the reaction of hydroxylamine with carboxylic acids in neutral and acidic solutions. Jencks, *et al.*,[6] have shown that the equilibrium constant for acetohydroxamic formation, eq 3,

$$K = \frac{[\mathrm{CH_3CONHOH}][\mathrm{H_2O}]}{[\mathrm{CH_3COOH}]_{\mathrm{total}}[\mathrm{NH_2OH}]_{\mathrm{total}}} \qquad (3)$$

has the value 1.46 at 25° and pH 7 (with $[\mathrm{H_2O}]$ taken as unity). The reaction is acid-catalyzed, but the extent of conversion to the hydroxamic acid decreases with lower pH. Lawlor[7] has reported that several metal ions, nickel(II) in particular, catalyze the formation of acetohydroxamic acid from acetic acid in aqueous solutions near neutral pH.

Although hydroxylamine is not a typical nucleophile in reactions at acyl carbon, its behavior is not unimportant in understanding these reactions. This base is a member of the class of α-effect nucleophiles,[8] which are nucleophiles possessing an unshared electron pair on the atom adjacent to the attacking atom; these nucleophiles commonly display a reactivity toward carbonyl and carboxyl carbon that is much greater than would be anticipated from their basicity. α effects have been widely discussed,[8,9] but are not yet well understood. The present paper reports kinetic and equilibrium studies of the reactions of hydroxylamine with acetic acid in aqueous solution, catalyzed by Ni(II) and by hydronium ion. These studies clarify the nature of these reactions and show that the easy detectability of hydroxamic acid formation is a consequence of an extremely high relative reactivity of hydroxylamine.

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[1] M. Calvin, "Chemical Evolution," Oxford University Press, New York, N. Y., 1969.

[2] T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 4.

[3] H. Morawetz and P. S. Otaki, *J. Amer. Chem. Soc.*, **85**, 463 (1963).

[4] A more realistic tentative rate equation would be $v = k_B[\mathrm{RCOO^-}]\cdot[\mathrm{R'NH_2}] + k_A[\mathrm{RCOOH}][\mathrm{R'NH_2}]$. The data in Table I of ref 3, when tested against this equation, are too sparse to permit k_A to be estimated, but chemical intuition suggests that $k_A \gg k_B$.

[5] T. Higuchi and T. Miki, *ibid.*, **83**, 3899 (1961); T. Higuchi, T. Miki, A. C. Shah, and A. K. Herd, *ibid.*, **85**, 3655 (1963); T. Higuchi, S. O. Eriksson, H. Uno, and J. J. Windheuser, *J. Pharm. Sci.*, **53**, 280 (1964).

[6] W. P. Jencks, M. Caplow, M. Gilchrist, and R. G. Kallen, *Biochemistry*, 2, 1313 (1963).

[7] J. M. Lawlor, *Chem. Commun.*, 404 (1967).

[8] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

[9] E. G. Sander and W. P. Jencks, *ibid.*, **90**, 6154 (1968); W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 107–111; G. Klopman, K. Tsuda, J. B. Louis, and R. E. Davis, *Tetrahedron*, **26**, 4549 (1970); J. E. Dixon and T. C. Bruice, *J. Amer. Chem. Soc.*, **93**, 3248 (1971).

Experimental Section

Materials. Unless otherwise stated, all chemicals were analytical reagent grade and were used directly. Acetohydroxamic acid was prepared by the procedure of Wise and Brandt[10] modified as follows: 56.1 g of potassium hydroxide in 150 ml of methanol was slowly added to 46.7 g of hydroxylamine hydrochloride dissolved in 240 ml of methanol, both solutions being brought to 40° before the addition. The mixture was cooled in an ice–water bath during and after addition to precipitate potassium chloride, which was removed by filtration. Ethyl acetate, 30 g, was added to the reaction mixture and the resulting solution was allowed to stand at room temperature for 4 hr, when it was acidified with concentrated hydrochloric acid. The solvent was removed under reduced pressure, giving a syrupy residue, which was extracted with four 100-ml portions of boiling ethyl acetate. Crystals of acetohydroxamic acid were obtained from the ethyl acetate solution upon cooling; they were recrystallized twice from 10:1 ethyl acetate–methanol; mp 89° (lit.[11] 89–91°).

Ferric perchlorate hexahydrate, $Fe(ClO_4)_3 \cdot 6H_2O$ (G. F. Smith Co.), was used directly. All water was redistilled from alkaline permanganate. Ferric perchlorate stock solution (1.5 *M*) was prepared by dissolving 693.45 g of ferric perchlorate hexahydrate and 217 ml of 60% perchloric acid in enough water to make 1 l.; this solution was stored in the dark. Ferric perchlorate reagent solution (0.15 *M*) was prepared by diluting 100.0 ml of ferric perchlorate stock solution to 1 l. with absolute methanol. Acetic acid solutions were prepared by diluting glacial acetic acid (Dupont Chemical Co.) with water and standardizing by titration with standard sodium hydroxide. Standard buffer solutions were prepared according to Bates.[12] Ionic strength was adjusted with sodium chloride.

Apparatus. Spectral measurements were made with either a Cary Model 14 or Model 16 spectrophotometer fitted with thermostated cell compartments. pH measurements at 25° were made with either a Radiometer pH meter, Model 25, with scale expander and Sargent combination electrode (S-30072-15), or an Orion Model 801 pH meter with a Fisher high-temperature combination electrode (13-639-90). pH measurements at 90.5° were made with the Orion meter and Fisher electrode; for these measurements, standard buffer solutions and the sample solutions were equilibrated to 90.5° in jacketed beakers prior to and during pH measurement. Thermometers were calibrated against thermometers carrying an NBS certificate or an ASTM certificate.

Procedures. The kinetics of hydroxamic acid formation were studied in reaction mixtures prepared by mixing appropriate aliquots of reactant stock solutions and adjusting pH with concentrated sodium hydroxide or hydrochloric acid. Typical initial concentrations were 0.8 *M* hydroxylamine hydrochloride, 0.04 *M* nickel chloride, and 0.04 *M* acetic acid; when nickel was not present, the acetic acid concentration was brought to 0.4 *M*. Portions (3 ml) of the reaction mixture were sealed in glass ampoules and placed in a 90.5° water bath to initiate reaction. Ampoules were removed at recorded times and the reaction was quickly quenched by immersing the ampoules in a 2-propanol–Dry Ice bath. The ampoules were then stored at −5 to −10° until all samples from a reaction had been collected. They were brought to 25°, and 1.0 ml of the contents of an ampoule was added to 20 ml of ferric perchlorate reagent solution contained in a foil-wrapped flask. After 1 hr the absorbance at 530 nm (due to the ferric–hydroxamate complex) was measured.[13]

Rate constants for reactions at pH greater than 3 were calculated from initial velocity measurements, initial concentrations, and the rate equation. In this calculation the molar absorptivity of the ferric–hydroxamate complex is necessary. This was determined, under the analytical conditions, using samples of acetohydroxamic acid, giving ϵ_{530} 1.17×10^3.

For reactions at pH less than 3 the data were treated by plotting $\log (A_\infty - A_t)$ against time, where A_t is the absorbance of the colored solution for a sample withdrawn at time *t* and A_∞ is the absorbance for a sample that has reached equilibrium. Apparent first-order rate constants were obtained from the slopes of these plots. Equilibrium constants were calculated from A_∞ values, initial concentrations, and the molar absorptivity of the ferric–hydroxamate complex.

The hydrolysis of acetohydroxamic acid was studied in much the same way, portions of the reaction mixture being sealed in glass ampoules, withdrawn from the 90.5° bath at intervals, and the ferric–hydroxamate color developed. The initial concentration of acetohydroxamic acid was 1.5×10^{-3} *M*. Apparent first-order rate constants were obtained from plots of $\log (A_t - A_\infty)$ against time.

Results

Acid-Catalyzed Hydroxamic Acid Formation. The reaction of hydroxylamine with acetic acid was studied over the pH range 0.54–5.68 at 90.5°. The reaction is shown in eq 4. The equilibrium constant is defined by

$$CH_3COOH + NH_2OH \underset{k_r}{\overset{k_f}{\rightleftharpoons}} CH_3CONHOH + H_2O \quad (4)$$

eq 5, where the subscript eq,T denotes total molar con-

$$K = \frac{[CH_3CONHOH]_{eq,T}[H_2O]}{[CH_3COOH]_{eq,T}[NH_2OH]_{eq,T}} = \frac{k_f}{k_r} \quad (5)$$

centration of the bracketed compound at equilibrium. No assumptions about the ionic states of the species are made in this definition, so this equilibrium constant is pH dependent.

The rate constants k_f and k_r are also defined in terms of total concentrations, eq 6, so they are pH dependent.

$$v = k_f[CH_3COOH]_T[NH_2OH]_T - k_r[CH_3CONHOH]_T[H_2O] \quad (6)$$

From initial rate measurements at pH 3.50 the formation of acetohydroxamic acid was found to be first order in total acetic acid concentration and first order in total hydroxylamine concentration.[15]

Since only a very small fraction of the hydroxylamine present is consumed in the reaction, pseudo-first-order conditions hold, and the experimental first-order rate constant k_{obsd} is given by eq 7, where $[NH_2OH]_T$ repre-

$$k_{obsd} = k_f[NH_2OH]_T + k_r[H_2O] \quad (7)$$

sents total hydroxylamine concentration, *i.e.*, $[NH_2OH]_T = [NH_2OH] + [NH_3OH^+]$, which can be replaced by initial total hydroxylamine concentration. With these relationships k_f (and k_r) was determined at pH's less than 3. At pH's greater than 3, k_f was obtained from initial rate measurements; under these conditions the reverse reaction was not appreciable during the first few per cent of the forward reaction.

Figure 1 is the pH–rate profile for acetohydroxamic acid formation at 90.5°. Rate constants could not be obtained between pH 2 and 3 because of the lack of a suitable noninterfering buffer in this region. Studies with varying concentrations of reactants (see legend) showed no significant general catalysis by acetic acid or hydroxylamine. The dependence of k_f on pH can be accounted for with rate eq 8. Combining this equation

$$v_f = k_1[HOAc][NH_2OH][H^+]^2 + k_2[HOAc][NH_2OH][H^+] + k_3[HOAc][NH_2OH] \quad (8)$$

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(10) W. M. Wise and W. W. Brandt, *J. Amer. Chem. Soc.*, **77**, 1058 (1955).

(11) W. N. Fishbein, J. Daly, and C. L. Streeter, *Anal. Biochem.*, **28**, 13 (1969).

(12) R. G. Bates, *J. Res. Nat. Bur. Stand., Sect. A*, **66**, 179 (1962).

(13) Notari and Munson[14] have shown that the stability of the color of the ferric–hydroxamate solution is determined by the iron/hydroxylamine ratio, which should be at least 5 for optimum stability. In the present work this ratio was 4, with the result that an initial period of instability is followed by a fairly stable color, hence the 1-hr waiting period.

(14) R. E. Notari and J. W. Munson, *J. Pharm. Sci.*, **58**, 1060 (1969).

(15) Supporting data for this conclusion, and related observations, will be found in J. W. Munson, Ph.D. Dissertation, University of Wisconsin, Madison, 1971.

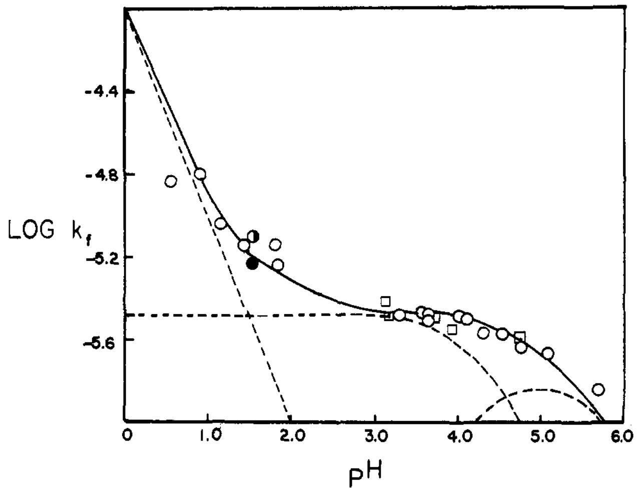

Figure 1. pH-rate profile for acetohydroxamic acid formation from acetic acid and hydroxylamine at 90.5° and ionic strength 1.2 *M*: (○) $[NH_2OH]_T$ = 0.80 *M*, $[HOAc]_T$ = 0.40 *M*; (◑) $[NH_2OH]_T$ = 0.40 *M*, $[HOAc]_T$ = 0.40 *M*; (●) $[NH_2OH]_T$ = 0.80 *M*, $[HOAc]_T$ = 0.86 *M*; (□) $[NH_2OH]_T$ = 0.80 *M*, $[HOAc]_T$ = 0.195 *M*.

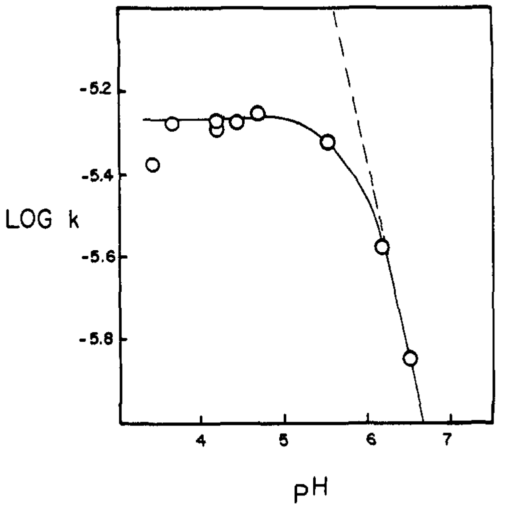

Figure 2. pH-rate profile for hydroxamic acid formation from succinic acid and hydroxylamine at 90.5°. $[NH_2OH]_T$ = 0.80 *M*, [succinic acid]$_T$ = 0.40 *M*. The slope of the dashed line is 1.0.

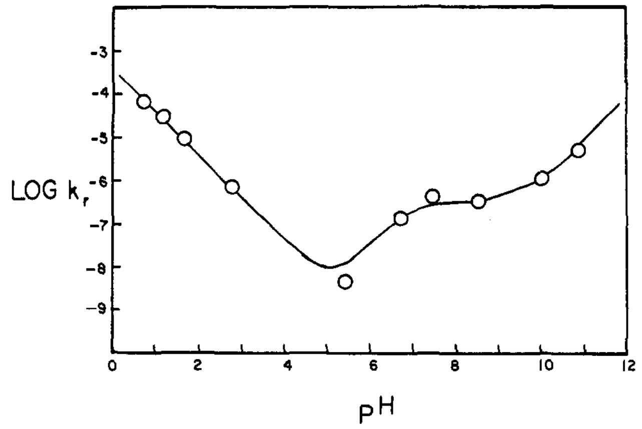

Figure 3. pH-rate profile for the hydrolysis of acetohydroxamic acid at 90.5° and ionic strength 1.2 *M*.

with the definitions $v_f = k_f[HOAc]_T[NH_2OH]_T$, $K_1 = [OAc^-][H^+]/[HOAc]$, and $K_2 = [NH_2OH][H^+]/[NH_3OH^+]$ gives eq 9.

$$k_f = \frac{K_2[H^+]}{(K_1 + [H^+])(K_2 + [H^+])} \times (k_1[H^+]^2 + k_2[H^+] + k_3) \quad (9)$$

The solid line in Figure 1 was calculated with eq 9, using independently determined values for the dissociation constants ($K_1 = 2.5 \times 10^{-5}$ and $K_2 = 7.4 \times 10^{-6}$ at 90.5° and ionic strength 1.2 *M*). The rate constants k_1, k_2, and k_3 were treated as adjustable parameters, the final values being $k_1 = 14.5\ M^{-3}\ \text{sec}^{-1}$, $k_2 = 0.45\ M^{-2}\ \text{sec}^{-1}$, and $k_3 = 1.2 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$. The dashed lines in Figure 1 show the contributions of the individual rate terms. Note that the k_1 term, though mechanistically second order in hydronium ion concentration, appears to be kinetically first order in this concentration, because the concentration of hydroxylamine conjugate base is decreasing in the same manner as hydronium ion concentration is increasing; similarly the k_2 term, though representing a reaction first order in $[H^+]$, appears to be independent of pH below pH 3.

The reaction of hydroxylamine with succinic acid was investigated briefly to determine the approximate relative reactivities of acetic acid and succinic acid with hydroxylamine. Second-order rate constants obtained from initial rate measurements are shown in Figure 2. At lower pH's a second slower reaction complicated the kinetics.[16] The line in Figure 2 has not been fitted with a rate equation. The important point here is that the rate constants obtained with succinic acid are similar in magnitude to those observed in the reaction with acetic acid.

Hydrolysis of Acetohydroxamic Acid. The rate constant k_r for the reverse of reaction 4 was measured over the pH range 0.73–10.80 at 90.5° by studying the hydrolysis of acetohydroxamic acid. This reaction goes essentially to completion, since the initial concentration of acetohydroxamic acid was 1.5×10^{-3} *M* and the solutions contained no acetic acid or hydroxylamine other than that generated in the hydrolysis. Apparent second-order constants were calculated by dividing the experimental first-order rate constant by water concentration, taking $[H_2O] = 55.5$ *M*. pH control was achieved with hydrochloric acid or sodium hydroxide at the extremes, and with glycine, phthalate, phosphate, or borate buffers at other pH's. Rate constants were extrapolated to zero buffer concentration; the buffer effect was small.[18] Some rate constants (not shown) were obtained from the kinetic treatment of the formation of acetohydroxamic acid from acetic acid; these constants, all below pH 3, agreed very well with those determined from the hydrolysis reaction. The pH-rate profile is shown in Figure 3. The line in this figure is drawn with the rate equation

$$v_r = k_a[CH_3CONHOH][H_2O][H^+] + k_b[CH_3CONHOH][H_2O][OH^-] + k_c[CH_3CONHO^-][H_2O][OH^-] \quad (10)$$

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(16) This reaction may have been the formation of the dihydroxamic acid. Cyclization of the monohydroxamic acid to form *N*-hydroxysuccinimide is a relatively fast reaction that has been studied at pH 9.5 by Notari.[17]

(17) R. E. Notari, *J. Pharm. Sci.*, **58**, 1064 (1969).

(18) No complications occur by hydroxamic acid formation from the buffer acids, because of the very low concentrations of hydroxylamine and because these acids are less reactive than is acetic acid.

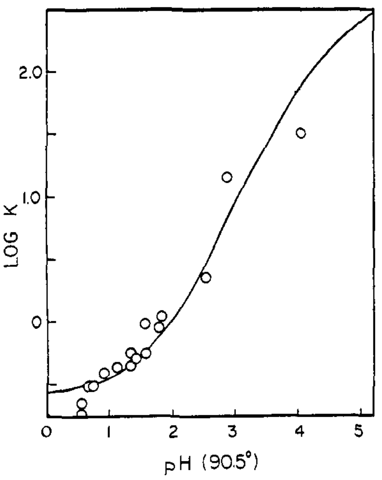

Figure 4. Variation of equilibrium constant for acetohydroxamic acid formation (eq 4) with pH at 90.5° and ionic strength 1.2 *M*. The line is calculated with the equation $K = k_f/k_r$ and eq 9 and 11.

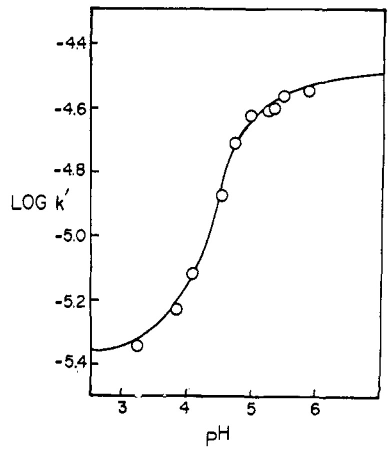

Figure 5. pH–rate profile for the formation of acetohydroxamic acid from acetic acid and hydroxylamine in the presence of nickel(II) at 90.5° and ionic strength 1.0 *M*; total concentrations were 0.035 *M* acetic acid, 0.80 *M* hydroxylamine, and 0.05 *M* nickel chloride.

which can be transformed into

$$k_r = \frac{v_r}{[CH_3CONHOH]_T[H_2O]} = \frac{k_a[H^+]^2}{K_a + [H^+]} + \frac{k_bK_w}{K_a + [H^+]} + \frac{k_cK_aK_w}{[H^+](K_a + [H^+])} \quad (11)$$

where K_a is the dissociation constant of acetohydroxamic acid and K_w, the autoprotolysis constant of water, was taken as 3.55×10^{-13} at 90.5°.[19] The values generated in developing the line in Figure 3 are $K_a = 1.5 \times 10^{-7}$, $k_a = 4.0 \times 10^{-4}\ M^{-2}\ sec^{-1}$, $k_b = 0.12\ M^{-2}\ sec^{-1}$, and $k_c = 2.5 \times 10^{-4}\ M^{-2}\ sec^{-1}$.

An equation for the equilibrium constant of reaction 4 can now be obtained by dividing eq 9 for k_f by eq 11 for k_r. When the rate constants and dissociation constants used to draw the solid lines in Figures 1 and 3 are put into this equation, the solid line in Figure 4, showing the expected variation of the equilibrium constant with pH, was calculated. The agreement with experimentally determined equilibrium constants is reasonable considering the difficulty of measuring the constant at very low pH (where the extent of conversion to acetohydroxamic acid is small) and above pH 4 (where excessive decomposition of hydroxylamine takes place because of the slowness of the hydroxamic acid formation). The calculated lines in Figures 1, 3, and 4 satisfactorily account for the data, but extrapolations below about pH 0.5 are questionable.

Nickel(II)-Catalyzed Hydroxamic Acid Formation. The initial concentrations used in studying the catalytic effect of nickel on acetohydroxamic acid formation were sodium acetate, 0.035 *M*; hydroxylamine hydrochloride, 0.8 *M*; and nickel chloride, 0.04 *M*. The ratio of hydroxylamine to nickel(II) is important in determining the maximum pH attainable. As pH is increased in solutions containing Ni(II), insoluble nickel hydroxide complexes are formed; in the absence of hydroxylamine, precipitation from solutions containing 0.04 *M* nickel chloride is first observed at pH 3–4 as the pH is increased by the addition of sodium hydroxide. In the presence of 0.8 *M* total hydroxylamine the pH of 0.04 *M* nickel chloride can be raised to about 7 (at 25°) before precipitation occurs, because of the formation of complexes between Ni(II) and hydroxylamine.

The order of reaction with respect to each reactant was investigated by the initial rate method, in which the concentration of one reactant is varied while all other concentrations are held constant. The slope of a log–log plot of initial velocity *vs.* initial concentration gives the order with respect to the reactant whose concentration has undergone variation. The slopes obtained for the indicated reactant at pH 5.2 and 90.5° were acetic acid, 1.0; hydroxylamine, 0.83; and nickel chloride, 0.69. These deviations from the anticipated values of unity are as qualitatively expected, since it is not possible in these solutions to vary either the hydroxylamine or the Ni(II) concentration without concomitantly varying the other, because of complex formation between these reactants.

Assuming the rate equation $v = k'[HOAc]_T[NH_2OH]_T$, the apparent second-order rate constant k' can be calculated from initial rate measurements. Figure 5 shows the pH dependence of these rate constants. The line in the figure was calculated on the basis of rate equation 12, which incorporates two of the terms from eq 8 plus a nickel-catalyzed reaction of acetate

$$v = k_2'[HOAc][NH_2OH][H^+] + k_3'[HOAc][NH_2OH] + k_{Ni}[OAc^-][NH_2OH][Ni^{2+}] \quad (12)$$

Proceeding as before gives

$$k' = \frac{K_2'}{(K_1' + [H^+])(K_2' + [H^+])} \times (k_2'[H^+]^2 + k_3'[H^+] + k_{Ni}K_1'[NiCl_2]_T) \quad (13)$$

In calculating the line in Figure 5 the dissociation constants K_1' and K_2' (for acetic acid and hydroxylammonium ion, respectively) were treated as adjustable parameters because of the complicating factor of nickel(II) complexation with hydroxylamine and acetate.[20] The

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(19) H. S. Harned and W. J. Hamer, *J. Amer. Chem. Soc.*, **55**, 2194 (1933).

(20) In the same way k_2' and k_3' must be adjustable parameters rather than quantities derived from the acid catalysis study. All of these quantities could have been sorted out with a knowledge of the stability constants of Ni(II) complexes with hydroxylamine and acetate at 90.5°; this would have been a major digression and would have added little to the present work.

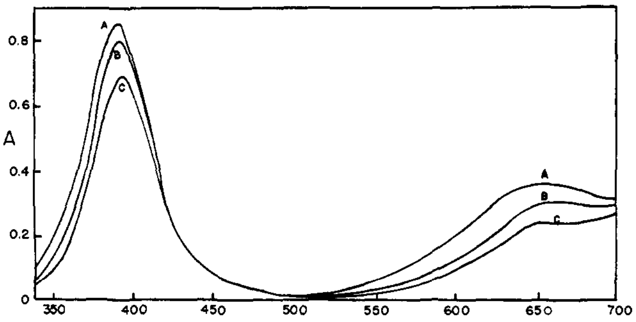


Figure 6. Absorption spectra of reaction solutions at 25°; the total concentrations are 1.1 *M* acetic acid, 0.10 *M* hydroxylamine, 0.125 *M* nickel chloride: (A) pH 6.10, (B) 5.10, (C) pH 3.62.

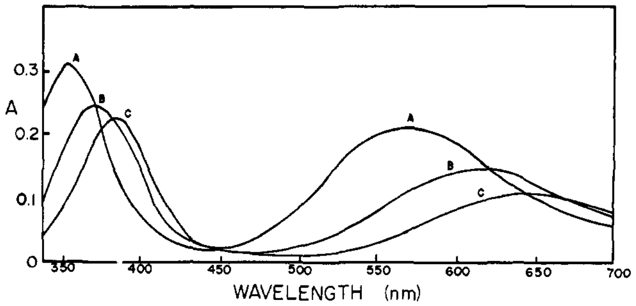


Figure 7. Absorption spectra of reaction solutions at 25°; the total concentrations are 0.04 *M* acetic acid, 0.80 *M* hydroxylamine, 0.04 *M* nickel chloride: (A) pH 6.70, (B) pH 5.44, (C) pH 4.29.

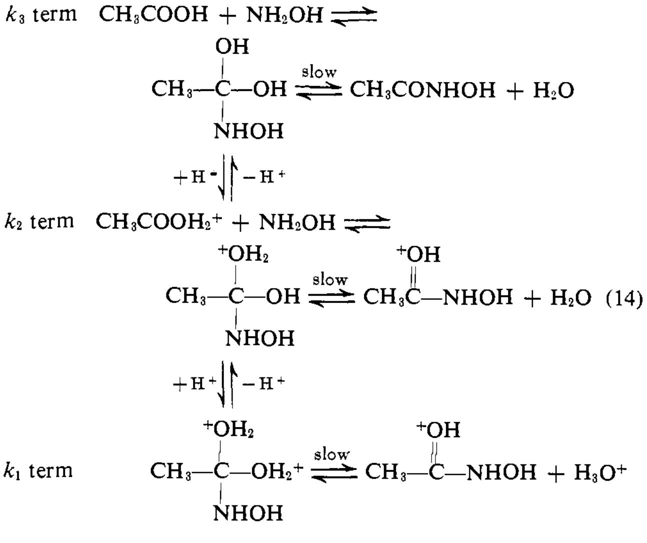
values obtained were $K_1' = 6.0 \times 10^{-5}$, $K_2' = 5.0 \times 10^{-6}$, $k_2' = 9.0 \times 10^{-2}\ M^{-2}\ \text{sec}^{-1}$, $k_3' = 2.5 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$, and $k_{\text{Ni}} = 7.2 \times 10^{-4}\ M^{-2}\ \text{sec}^{-1}$.

The nickel-catalyzed rate term of eq 12 does not agree in its form with that proposed by Lawlor,[7] who suggested a rate term of the form k[HOAc][NH_2OH] to account for a bell-shaped pH–rate profile. The difference between Lawlor's rate results and those in Figure 5 is a consequence of different concentration conditions. When these measurements were repeated using the initial concentrations 1.1 *M* acetic acid, 0.1 *M* hydroxylamine, and 0.125 *M* nickel chloride (Lawlor's conditions), a bell-shaped pH–rate curve was obtained, in agreement with Lawlor; the shape of this curve could be fitted by a rate term of the form suggested by Lawlor.

It is the concentration of hydroxylamine that determines the apparent nature of the rate equation in this reaction. The distinctions between solutions prepared with Lawlor's concentration conditions and our conditions can be readily seen by eye, and are shown graphically in the absorption spectra of Figures 6 (Lawlor's conditions) and 7 (our conditions). Three nickel(II)–hydroxylamine complexes are known,[21] with the Ni(II): NH_2OH stoichiometries 1:2, 1:4, and 1:6. The spectra in the reaction solutions are consistent with the conclusion that under Lawlor's conditions essentially only the 1:2 complex is present, whereas with our conditions increasing pH increases the concentration of free hydroxylamine to levels where the 1:4 and finally the 1:6 complex is formed. This observation does not, however, account for the difference in the forms of the rate equations under the two conditions. One possibility is that the rate term contains the product [OAc^-][NH_2OH] under all conditions (that is, it is a Ni(II)-catalyzed reaction of acetate ion), and that the decreased catalytic effectiveness on the alkaline side under Lawlor's conditions is a consequence of the formation of mixed Ni(II)–hydroxylamine–hydroxide complexes, which should be less effective catalytically than any of the Ni(II)–hydroxylamine complexes. When the ratio of hydroxylamine to nickel is large enough to allow formation of 1:4 and 1:6 complexes, displacement of H_2O or NH_2OH by OH^- is less favored, and the catalytic activity is not decreased at higher pH.

Discussion

Acid Catalysis. Each of the rate terms in rate eq 8 for the acid-catalyzed formation of acetohydroxamic acid can be written in different, but kinetically equivalent, forms. Thus the product [HOAc][NH_2OH] is kinetically equivalent to [OAc^-][NH_2OH][H^+] and to [OAc^-][NH_3OH^+]. The last of these is chemically unlikely for this reaction, and the first two express much the same mechanistic idea, namely, an attack by neutral hydroxylamine on neutral acetic acid. Similarly, the term containing the product [HOAc][NH_2OH][H^+] is equivalent to [H_2OAc^+][NH_2OH], and could reflect nucleophilic attack by hydroxylamine on protonated acetic acid.[22] This type of argument is unconvincing, however, when applied to the rate term containing the product [HOAc][NH_2OH][H^+]^2, which is equivalent to several other forms, such as [H_2OAc^+][NH_2OH][H^+], [H_2OAc^+][NH_3OH^+], and [H_2OAc^{2+}][NH_2OH]. Rate equation 8 can be accounted for by postulating the formation of a tetrahedral intermediate whose decomposition is the rate-determining step. This idea is shown in eq 14.[24] The k_2 term could arise by alternative pathways as shown. The positions of protonation in eq 14



$$
\begin{aligned}
&k_3 \text{ term} \quad CH_3COOH + NH_2OH \rightleftharpoons \\
&\qquad CH_3-\overset{\displaystyle OH}{\underset{\displaystyle NHOH}{C}}-OH \overset{\text{slow}}{\rightleftharpoons} CH_3CONHOH + H_2O \\
&\qquad +H^+ \downarrow\uparrow -H^+ \\
&k_2 \text{ term} \quad CH_3COOH_2^+ + NH_2OH \rightleftharpoons \\
&\qquad CH_3-\overset{\displaystyle ^+OH_2}{\underset{\displaystyle NHOH}{C}}-OH \overset{\text{slow}}{\rightleftharpoons} CH_3\overset{\displaystyle ^+OH}{\overset{\|}{C}}-NHOH + H_2O \qquad (14) \\
&\qquad +H^+ \downarrow\uparrow -H^+ \\
&k_1 \text{ term} \quad CH_3-\overset{\displaystyle ^+OH_2}{\underset{\displaystyle NHOH}{C}}-OH_2^+ \overset{\text{slow}}{\rightleftharpoons} CH_3-\overset{\displaystyle ^+OH}{\overset{\|}{C}}-NHOH + H_3O^+
\end{aligned}
$$

are not intended to be definitive, but merely to show a tautomeric possibility.

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[21] M. T. Falqui, G. Ponticelli, and F. Sotgui, *Ann. Chim.* (*Rome*), **56**, 464 (1966).

[22] Since the pK_a for protonated acetic acid is -6.1,[23] the equivalent second-order rate constant for this term becomes about 5.7×10^5 $M^{-1}\ \text{sec}^{-1}$.

[23] E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 223 (1963).

[24] *O*-Acylhydroxylamine formation has been demonstrated as an intermediate step in hydroxamic acid formation from activated acyl compounds by Jencks[25] and, less directly, from ethyl acetate by Notari.[26] On the basis of the present work, there seems to be no necessity to postulate *O*-acetylhydroxylamine formation in the reaction with acetic acid.

[25] W. P. Jencks, *J. Amer. Chem. Soc.*, **80**, 4581, 4585 (1958).

[26] R. E. Notari, *J. Pharm. Sci.*, **58**, 1069 (1969).

This scheme indicates that the hydrolysis of acetohydroxamic acid should include a rate term second order in hydrogen ion (reverse of the k_1 term). The experimental results do not reveal such a term. If, in the hydrolysis reactions, the formation of the tetrahedral intermediate is rate determining, it is reasonable that the attack of H_3O^+ on protonated acetohydroxamic acid should be less favored than the attack by H_2O. In the region below pH 1, the formation reaction is dominated by the k_1 term, whereas the hydrolysis is occurring primarily *via* the reverse of the k_2 term. These represent different reactions (not alternative mechanisms of a single reaction), each subject to an equilibrium configuration, so this interpretation is consistent with the requirement of microscopic reversibility. The experimental equilibrium constant is a composite quantity.

A reaction pathway involving acetic anhydride as an intermediate, analogous to the reactions of polycarboxylic acids studied by Higuchi,[5] is ruled out by the first-order dependence on acetic acid; the similar rates of reaction for acetic and succinic acids suggest that succinic acid also reacts directly rather than *via* succinic anhydride. Ethyl acetate reacts at about the same rate as does acetic acid in the pH range 3–5.5,[15] which again suggests no unusual behavior by the acid substrate.[27]

The suggestion that decomposition of a tetrahedral intermediate is rate determining in the acetic acid–hydroxylamine condensation is consistent with a recent classification by Fersht and Jencks;[28] their class III of acyl-transfer reactions includes those of weakly basic nucleophiles and substrates with poor leaving groups. Such reactions are characterized by high β values (slopes of Brønsted-type plots) with respect to the nucleophile and the leaving group. Fersht and Jencks have also constructed a Brønsted plot for reactions of nucleophiles with acetic acid (the rate constants being calculated from the equilibrium constants and the rate constants for the reverse reactions). It is interesting to compare the directly measured rate constant for acetohydroxamic acid formation with this derived plot (Figure 5 of ref 28). The appropriate rate constant is k_3 of eq 8, which has the value 1.2×10^{-5} M^{-1} sec^{-1} at 90.5°. If the temperature dependence of this rate constant is normal, its expected value at 25° will be 10^{-8}–10^{-7} M^{-1} sec^{-1}. For a nucleophile of $pK_a = 6.0$ (hydroxylamine at 25°), the Brønsted plot predicts a value of about 10^{-17}–10^{-16} M^{-1} sec^{-1}. This is an α effect with a vengeance; probably this comparison is not a valid one. (Typical positive deviations by α-effect nucleophiles from Brønsted plots are one to two orders of magnitude.) It seems clear, however, that the observation of hydroxamic acid formation is possible because of a peculiarly high reactivity of hydroxylamine, and not because of special behavior by the acid substrate.

Nickel(II) Catalysis. Under our concentration conditions, the final term in eq 12 appears to describe the catalytic behavior of Ni(II) on acetohydroxamic acid formation. The product $k_{Ni}[Ni^{2+}] = k_{Ni}'$ is about equal to k_3' in this rate equation; that is, in the presence of 0.04 *M* nickel chloride, acetate ion is about as good a substrate toward hydroxylamine as is acetic acid. Presumably Ni(II) transforms the acetate anion, by coordination,[29] into a better substrate, and thus provides a new reaction pathway. If Lawlor's representation of the rate equation were correct, then under his conditions a nickel(II)-catalyzed term of the k_2' form (see eq 12), with Ni^{2+} in place of H^+, would be operative, the nickel presumably aiding the decomposition of the tetrahedral intermediate. As described earlier, an alternative explanation can be given, and we find no compelling evidence for Ni(II)-catalyzed reations, analogous to those of eq 14, in which neutral acetic acid is the substrate and Ni(II) takes the place of H^+. In fact, the observed second-order rate constants for acetohydroxamic acid production are unaffected by the presence of 0.04 *M* $NiCL_2$ below pH 2; these points fall along the line for acid catalysis in Figure 1, showing that nickel(II) does not catalyze these reactions.

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[27] Actually acetic acid reacts slightly faster than ethyl acetate over this pH range, an interesting observation on the "activation" of acyl groups. Above pH 5.5 the base-catalyzed reaction of ethyl acetate predominates, and below pH 3 the incursion of eq 4 complicates the kinetics.

[28] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 92, 5442 (1970).

[29] The stability constant for the complex $NiOAc^+$ is 62.5 at 25°: K. B. Yatsimirskii and V. P. Vasil'ev, "Instability Constants of Complex Compounds," Van Nostrand, Princeton, N. J., 1960, p 152. Catalysis by the 1:6 complex requires displacement of hydroxylamine by acetate.