

Addition of Water to 1-Alkynylamines. Kinetics and Mechanism

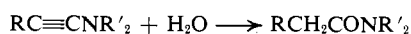
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Abstract: The addition of water to $\text{PhC}\equiv\text{CNR}'_2$ is investigated in water-dioxane (10.6:1) by stopped flow spectrophotometry. In basic medium the reaction is general acid catalyzed with a Brønsted α of 0.74. This behavior indicates rate-determining proton transfer to carbon. This conclusion is supported by the solvent deuterium isotope effect $k(\text{H}_2\text{O})/k(\text{D}_2\text{O})$ of approximately 4 and by the effect of substituents R' . The highly negative entropy of activation of the reaction in which water is the general acid (≈ -39 eu) is in line with the slow step being essentially an ionization. Proton transfer to ynamines is faster than to acetylenic ethers by approximately six powers of ten. It is also much faster to ynamines than to enamines. In acetic acid-sodium acetate buffer the rate is 10^4 times slower than expected from a Brønsted extrapolation. This retardation is ascribed to complex formation between ynamine and acetic acid, which interpretation is supported by an uv shift. In this complex nitrogen is protonated; $K_a \approx 10^{-5}$ M from kinetic as well as spectrophotometric data. Subsequently, this proton is transferred to carbon in a reaction catalyzed by either acetic acid or hydroxyl ions. The acetic acid catalysis could be an example of bifunctional catalysis.

In earlier papers we reported on the mechanism of addition of water to the triple bond of oxygen-² and sulfur-substituted³ acetylenes. In acidic and neutral aqueous solution these reactions are general acid catalyzed, the first step being a slow proton transfer. 1-Alkenylamines, enamines, add water *via* an analogous mechanism but only in basic solution.⁴

The addition of water to nitrogen-substituted acetylenes, ynamines, is the subject of the present paper. The literature about ynamines up to the middle of 1969 is covered in a review by Viehe.⁵ In the reaction with water an amide is formed



As the rate of addition in aqueous solution is very fast, stopped flow spectrophotometry was used to study this reaction.

Experimental Section

A modified Durrum-Gibson stopped flow instrument was used. We chose 1,4-dioxane as solvent for the ynamines. Other solvents led to a higher temperature rise on mixing with water. The use of dioxane introduced a few problems.

1. The regular mixing ratio of 1:1 would give a reaction medium of 50 vol. % dioxane. Comparison of our results with studies on other acetylenes would then become very difficult because these studies were carried out in water. Therefore, by a simple lever construction the mixing ratio of dioxane and water was changed to a lower value, *viz.* 1:10.6. Thus, the dioxane content was only 8.6 vol. %. This modification increased the dead time from 1 to 10 msec.

2. When mixing water with dioxane a temperature rise occurs which is not corrected sufficiently fast by the constant temperature bath surrounding cuvette and syringes because of the high rate of reaction. A cuvette assembly was constructed with a built-in glass encapsulated thermistor for temperature measurement.

3. Dioxane removed every lubricant used to prevent leakage between plunger and syringe wall. Therefore, the original plungers

were replaced by Teflon plungers with a variable diameter. Leakage was prevented by increasing the diameter as far as necessary.

A Beckman DU monochromator was used. With this set up it was not possible to measure rates with sufficient accuracy below 240 nm. Since absorption maxima of ynamines with only aliphatic substituents are below 240 nm, we used 1-dialkylamino-2-phenylacetylenes which have an absorption maximum around 290 nm. In this region the molar absorption coefficients of the corresponding amides are less than 10% of those of the ynamines.

All reactions were first order to at least 75% conversion. All first-order rate constants given are averages of five measurements. The standard deviation of the mean is less than 5% except for the rates in the $\text{H}_2\text{PO}_4^-/\text{HPO}_4^{2-}$ buffer solutions which are very high. Here a standard deviation of 30–40% is a reasonable estimate.

The ynamines were prepared as described by Viehe⁵ from phenylchloroacetylene and lithium amides. Freshly distilled samples were used for the kinetic measurements. 1,4-Dioxane was freshly distilled before use from potassium hydroxide in a nitrogen atmosphere. The solvent water was doubly distilled in a quartz apparatus. Deuterium oxide (Merck) with a deuteration grade of over 99.5% was used. Sodium perchlorate (p.a.) was dried for 24 hr *in vacuo* at room temperature; in this way the monohydrate is obtained.⁶ For the measurements in D_2O anhydrous sodium perchlorate was necessary; the water was removed by drying for 24 hr at 200°.⁶

Results and Discussion

The reaction was studied in a variety of weakly basic aqueous solutions and in acetic acid-sodium acetate buffers. As there appeared to be a sharp distinction in the behavior under basic and acidic conditions, these classes will be treated separately.

Reactions in Basic Medium. The rate of addition of water to 1-piperidino-2-phenylacetylene was measured in four buffers as well as in sodium hydroxide dissolved in 8.6 vol. % dioxane-water. The buffer ratio was 1:1 except for $\text{HCO}_3^-/\text{CO}_3^{2-}$ where 3:1 and 10:1 were also used. The reactions showed pseudo-first-order behavior. In each of the buffer series the rate constants obey the equation

$$k_1 = k_0 + k_{\text{HA}}[\text{HA}] \quad (1)$$

Figure 1 shows a plot of the first-order rate constant measured in the carbonate buffer solutions against the bicarbonate concentration. Points of all three dif-

(6) M. Vlatković and A. H. W. Aten, *J. Inorg. Nucl. Chem.*, **24**, 139 (1962).

(1) Part of the Ph.D. Thesis of W. F. Verhelst, University at Utrecht, 1973.

(2) E. J. Stamhuis and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **82**, 394 (1963), and references cited therein.

(3) H. Hogeveen and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **82**, 410 (1963), and references cited therein.

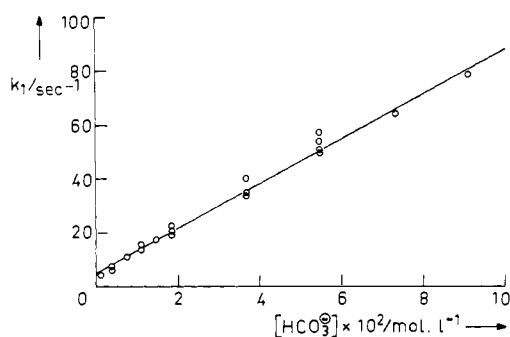
(4) E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30**, 2156 (1965).

(5) H. G. Viehe in "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 12.

Table I. Rate Data of the Reaction of 1-Piperidino-2-phenylacetylene with Water in Buffered and in Sodium Hydroxide Solutions^a

Acid	pK _a ^b	p ^c	q ^c	[HA] × 10 ³ , M	n ^d	k _{HA} , (M sec) ⁻¹	k _{H₂O} × 10 ² , (M sec) ⁻¹
H ₂ PO ₄ ⁻	7.2	2	3	0.91–4.57	7	(8 ± 1) × 10 ⁴	80 ± 63
HCO ₃ ⁻	10.2	1	3	0.91–91	18	(83 ± 2) × 10	9 ± 1
H ₃ BO ₃	9.2	2 ^e	4 ^e	0.91–22.8	8	194 ± 5	5.7 ± 0.2
HPO ₄ ²⁻	12.4	1	4	3.66–27.4	7	23.1 ± 1.8	4.3 ± 0.1
H ₂ O	15.7	2	1	56	5	(2.0 ± 0.1) × 10 ⁻² ^f	

^a Solvent 8.6% v/v 1,4-dioxane–water; temperature 26.0°; ionic strength 0.30 M, NaClO₄ added. ^b The dissociation constants are generally not known in the medium used here; however, corrections are unimportant. ^c Statistical factors in the Brønsted equation. ^d Number of first-order rate constants. ^e Based upon the equilibrium H₃BO₃ + H₂O ⇌ (HO)₂B⁻ + H⁺. ^f Obtained by interpolation from the data in Figure 2 at 0.183 M NaOH.

**Figure 1.** The relation between the first-order rate constant of the reaction of 1-piperidino-2-phenylacetylene with water and the hydrogen carbonate ion concentration; data for various acid–salt ratios.

ferent acid–salt ratios are included. The plot does not deviate significantly from a straight line. Apparently, variations in acid–salt ratio, *i.e.*, in hydronium ion activity, do not find expression in deviations from the straight line. Obviously, in this range the contribution of protons to the catalysis, if present, is negligible compared with the contribution of the undissociated acid.

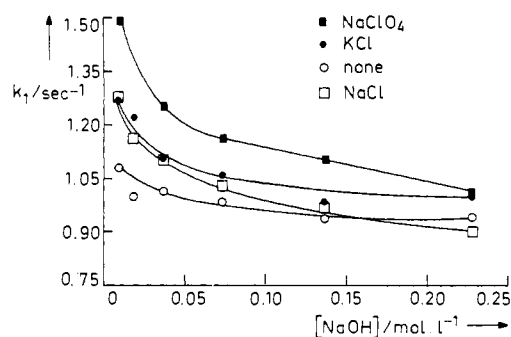
The constant k_0 in eq 1 probably expresses the contribution of the solvent water acting as proton donor. So, the experimental first-order rate constant can be written as

$$k_1 = k_{H_2O}[H_2O] + k_{HA}[HA] \quad (2)$$

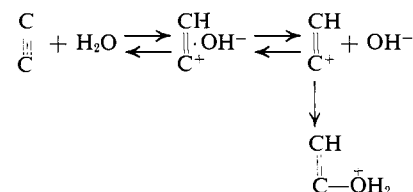
Values for the coefficients in this equation as well as other relevant data are given in Table I.

In sodium hydroxide solutions the only acids present are water and hydronium ions. As the hydronium ions do not contribute to the catalysis in carbonate buffers, the catalysis due to these ions can certainly be neglected in the much more basic sodium hydroxide solutions. Therefore, the rate is expected to be independent of the sodium hydroxide concentration. Remarkably, a rate decrease is observed with increasing hydroxide concentration (Figure 2), even when salts are added to keep the ionic strength at a constant value. The curves are somewhat reminiscent of a special salt effect⁷ but in downward instead of upward direction. A reversed special salt effect could be the result of increased ion-pair return by an increased hydroxyl ion concentration or simply a kind of common ion effect. Another explanation of the observed salt effect might be

(7) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2767 (1956).

**Figure 2.** The relation between the first-order rate constant of the reaction of 1-piperidino-2-phenylacetylene with water and the sodium hydroxide concentration; different salts added to keep the ionic strength at a constant value of 0.30 M, except for one series. Solvent 8.6% v/v 1,4-dioxane–water; temperature 26.0°.

found in terms of change in water structure and, accordingly, in dynamic water acidity.⁸

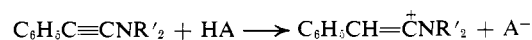


Application of the Brønsted equation⁹

$$k_{HA}/p = G[(q/p)K_a]^\alpha$$

leads to a coefficient α of 0.74, correlation coefficient 0.998. We are not aware of reliable Brønsted α values for other hetero-substituted acetylenes. From rate constants of only two acids, one of which is H₃O⁺, an α value of 0.5 appears for alkoxyethyne² as well as for ethylthioethyne.³ For enamines⁴ α amounts to approximately 0.6.

The observed general acid catalysis strongly points to a rate-determining proton transfer from acid to triple bond carbon. In this respect the reaction is analogous



to the acid-catalyzed addition of water to 1-alkynyl ethers² and sulfides.³

A mechanism involving rate-determining proton transfer is supported by the value of the solvent deute-

(8) Compare for dynamic water basicity: (a) F. Hibbert and F. A. Long, *J. Amer. Chem. Soc.*, **94**, 7637 (1972); (b) L. Menninga and J. B. F. N. Engberts, *J. Phys. Chem.*, **77**, 1271 (1973).

(9) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 219. In this calculation the point for H₃BO₃ was omitted because it deviates appreciably. When this point is included, $\alpha = 0.71$.

rium isotope effect. The experimental data are given in Table II. The ratio $k_1(\text{H}_2\text{O})/k_1(\text{D}_2\text{O})$ is appreciably

Table II. First-Order Rate Constants^{a,b} and the Deuterium Isotope Effect^b of the Reaction of Three Ynamines with Water and with Deuterium Oxide

Compd	$k_1(\text{H}_2\text{O}),$ sec ⁻¹	$k_1(\text{D}_2\text{O}),$ sec ⁻¹	$k_1(\text{H}_2\text{O})/$ $k_1(\text{D}_2\text{O})$
$\text{C}_6\text{H}_5\text{C}\equiv\text{CN}(\text{CH}_2)_5$	1.03	0.23	4.5
$\text{C}_6\text{H}_5\text{C}\equiv\text{CN}(n\text{-C}_3\text{H}_7)_2$	1.46	0.33	4.4
$\text{C}_6\text{H}_5\text{C}\equiv\text{CN}(i\text{-C}_3\text{H}_7)_2$	1.99	0.61	3.3

^a Solvent 8.6% v/v 1,4-dioxane–water or 1,4-dioxane–deuterium oxide; temperature 26.0°; $[\text{NaOH}], 0.183\text{ M}$; ionic strength 0.30 M , by adding sodium perchlorate. ^b Standard deviation in the isotope effect 7%, or approximately 0.3.

larger than one, indicating slow proton transfer from water to ynamine.

Also the effect of the substituents R' on nitrogen is consistent with an electrophilic attack on the ynamine. The first-order rate constants $k_1(\text{H}_2\text{O})$ were measured for seven ynamines in 0.183 M sodium hydroxide solution (Table III).

Table III. First-Order Rate Constants^a of the Reaction of Ynamines, $\text{C}_6\text{H}_5\text{C}\equiv\text{CNR}'_2$, with Water; Sum of Polar Substituent Constants

NR'_2	$k_1(\text{H}_2\text{O}), \text{sec}^{-1}$	$\Sigma\sigma^*_{R'}$ ^b
$\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$	0.015	0.67 ^c
$\text{N}(\text{CH}_3)_2$	0.75	0.00
$\text{N}(\text{CH}_2)_5$	1.03	-0.14 ^c
$\text{N}(\text{C}_2\text{H}_5)_2$	2.50	-0.20
$\text{N}(\text{C}_2\text{H}_5)_2$ - $n\text{-C}_3\text{H}_7$	2.19	-0.22
$\text{N}(n\text{-C}_3\text{H}_7)_2$	1.47	-0.23
$\text{N}(i\text{-C}_3\text{H}_7)_2$	1.88	-0.38

^a Solvent 8.6% v/v 1,4-dioxane–water; temperature 26.0°; $[\text{NaOH}], 0.183\text{ M}$; ionic strength 0.30 M , by adding sodium perchlorate. ^b Values taken from ref 10, p 619. ^c Values deduced from known $\text{p}K_a$ and Hall equation (ref 11).

A least-squares analysis of these rate constants applying Taft's equation¹⁰

$$\log k_{R'} = \rho^* \Sigma\sigma^*_{R'} + \text{constant} \quad (3)$$

gives a ρ^* value of -2.2. The absolute value of ρ^* is not very reliable because it depends mainly on the rate of the morpholino derivative. The polar substituent constant for the alkyl ether part of the morpholino ring, $(\text{CH}_2\text{CH}_2)_2\text{O}$, was obtained by substituting the known $\text{p}K_a$ of morpholine in the Hall equation¹¹

$$\text{p}K_a = -\rho^* \Sigma\sigma^*_{R'} + \text{constant} \quad (4)$$

which relates basicity of amines $\text{NR}^1\text{R}^2\text{R}^3$ to the sum of the polar substituent constants of the groups R . The value of $\sigma^* = 0.67$ might be influenced by a field effect of the oxygen on the nitrogen lone pair of electrons.¹² However, the conclusion seems justified that

(10) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(11) H. K. Hall, *J. Amer. Chem. Soc.*, **79**, 5441 (1957).

(12) J. Clark and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **18**, 295 (1964).

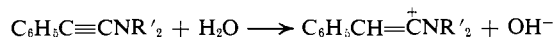
electron-withdrawing groups decrease the rate of reaction.

For three ynamines $\text{C}_6\text{H}_5\text{C}\equiv\text{CNR}'_2$ the rate constant measurements of Table III were extended to six temperatures ranging from 26.0 to 48.8°. After conversion to second-order rate constants $k_{\text{H}_2\text{O}}$ activation parameters were calculated by the equation

$$k_{\text{H}_2\text{O}} (\text{mol/l.}) = (RT/Nh)e \exp[(-\Delta H^\ddagger/RT) + (\Delta S^\ddagger/R)]$$

R'_2	$(n\text{-C}_3\text{H}_7)_2$	$(i\text{-C}_3\text{H}_7)_2$	$(\text{CH}_2)_5$
$\Delta H^\ddagger, \text{kcal/mol}$	8.1 ± 0.3	7.9 ± 0.3	9.1 ± 0.5
$\Delta S^\ddagger, \text{eu}$	-39 ± 1	-39 ± 1	-36 ± 1

The highly negative values of ΔS^\ddagger are in line with the slow step being essentially an ionization¹³



Our data do not allow a direct comparison of the rates of these phenylacetylenic nitrogen compounds with those of the earlier investigated alkylacetylenic oxygen compounds. The retarding substituent effect of a β -phenyl group in vinyl ether hydrolysis is in the order of 10^2 .¹⁴ This effect is predominantly the result of conjugative stabilization of the initial state and not a result of transition state behavior. Since vinyl ether and ynamine hydrolysis have similar Bronsted α values and, therefore, probably comparable transition states, the β -phenyl effect in ynamines might be expected also to be 10^2 or even more. An exception would be the occurrence of phenyl participation. However, phenyl participation seems to be rare in electrophilic additions.¹⁵ A comparison of the data for the H_2PO_4^- catalyzed reactions indicates that ynamines react faster than acetylenic ethers² by at least six powers of ten. The reason might be a better stabilization of the transition state, which resembles a vinyl cation, because of the decreased electronegativity of nitrogen relative to oxygen.



However, there might be an additional reason for the high rate of proton addition to ynamines as appears from its ratio to enamines. The rate constant $k_{\text{H}_2\text{O}}$ is 2000 times larger for 1-piperidino-2-phenylacetylene than for 1-piperidino-2-methyl-1-propene.^{4,16} For $k_{\text{H}_3\text{BO}_3}$ this ratio is 20,000. Taking account of the phenyl effect the ratio is even larger. Yates, *et al.*,¹⁵ showed that the generally very small ratio $k_{\text{acetylene}}/k_{\text{olefin}}$ in electrophilic additions is increased to around one when changing from nonaqueous to aqueous solution. Although part of this effect might be due to initial state behavior, by far the larger part must be the result of a relatively more favorable solvation of the transition state in additions to acetylenes. Apparently, this effect is enhanced by the nitrogen atom. A similar enhancement, although to a lesser extent, is caused by an oxygen atom. The ratio of $k_{\text{H}_2\text{O}}$ for ethoxyethyne² and ethoxyethene¹⁷ amounts to 180.

(13) Compare, *e.g.*, ref 9, p 138.

(14) A. J. Kresge and H. J. Chen, *J. Amer. Chem. Soc.*, **94**, 2818 (1972).

(15) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H. Leung, and R. McDonald, *J. Amer. Chem. Soc.*, **95**, 160 (1973).

(16) W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *J. Org. Chem.*, **32**, 1111 (1967).

(17) A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Amer. Chem. Soc.*, **93**, 413 (1971).

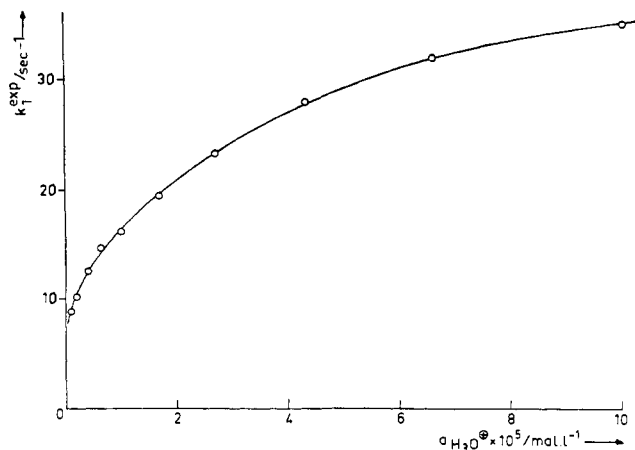


Figure 3. The relation between the first-order rate constant of the reaction of 1-piperidino-2-phenylacetylene with water and the hydronium ion activity at constant acetic acid concentration of 0.046 *M* and an ionic strength of 0.90 *M*. Solvent 8.6% v/v 1,4-dioxane-water; temperature 26.0°. [Activity coefficients for univalent electrolytes in solutions of 0.30 and 0.90 *M* ionic strength are nearly equal: H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958.]

Reactions in Acetic Acid-Sodium Acetate Buffers.

From the Brønsted relation derived in the preceding section the catalytic constant for acetic acid in the reaction of 1-piperidino-2-phenylacetylene with water can be estimated to be $4.6 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$. Therefore, neglecting catalysis by protons and also neglecting a possible deviation of acetic acid from the Brønsted plot, the first-order rate constant in 0.02 *M* acetic acid solution would be 10^5 sec^{-1} . Actually, in such solutions of 1-piperidino-2-phenylacetylene we have determined rate constants with values of approximately 10 sec^{-1} . Thus the reaction with water in acetic acid-sodium acetate buffer solutions proceeds approximately 10^4 times slower than expected, indicating that its mechanism is different from that in basic medium.

The rate of addition of water to 1-piperidino-2-phenylacetylene has been measured in various acetic acid-sodium acetate buffers dissolved in 8.6 vol. % aqueous dioxane. The reactions showed pseudo-first-order behavior. In Figures 3 and 4 these rate constants are plotted vs. hydronium ion activity and acetic acid concentration,¹⁸ respectively. The leveling of the plot in Figure 3 may be understood in terms of protonation of the ynamine. Indeed, the pK_a of an ynamine can be expected to have a value of approximately 5. This estimate is obtained from the Hall equation¹¹ which relates pK_a of an amine $\text{NR}^1\text{R}^2\text{R}^3$ to the sum of the polar substituent constants

$$pK_a = -3.30\sum\sigma^*_R + 9.61 \quad (5)$$

With polar substituent constants for $\text{C}_6\text{H}_5\text{C}\equiv\text{C}$ and $(\text{CH}_2)_5$ of 1.35¹⁹ and -0.14 ,²⁰ respectively, the calculated pK_a is 5.6. The actual value may be somewhat

(18) From the association constant in water the fraction of dimer acetic acid is calculated to be smaller than 1%: G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," Reinhold, New York, N. Y., 1960, p 369.

(19) J. Shorter in "Advances in Linear Free Energy Relationships," N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N. Y., 1972, p 76.

(20) Note c of Table III.

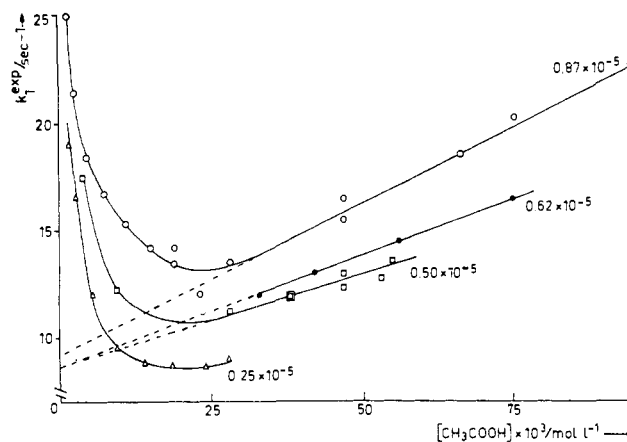
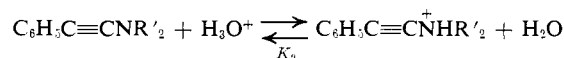


Figure 4. The relation between the first-order rate constant of the reaction of 1-piperidino-2-phenylacetylene with water and the acetic acid concentration at hydronium ion activities given at the right-hand side of the lines. The ionic strength has a constant value of 0.30 *M*. Solvent 8.6% v/v 1,4-dioxane-water; temperature 26.0°.

lower because of mesomeric interaction between nitrogen and triple bond.

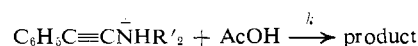
Thus, the first step of the reaction could be the equilibrium



The fraction protonated ynamine is $a_{\text{H}_3\text{O}^+}/(K_a + a_{\text{H}_3\text{O}^+})$. If the rate constant k is proportional to this fraction exclusively, there should be a linear relation between $a_{\text{H}_3\text{O}^+}$ and $a_{\text{H}_3\text{O}^+}/k_1$. This condition is met except for low hydronium ion activities. From the intercept a preliminary value for K_a of $2.5 \times 10^{-5} \text{ M}$ is found.

The explanation of Figure 4 is less obvious. We first discuss the region to the right-hand side of the minima. In this region and at a constant hydronium ion activity the rate linearly depends on the acetic acid concentration. The slope of this straight line is higher at a higher hydronium ion activity in accordance with the hypothesis that the protonated fraction determines the rate of reaction. In this case the hypothesis requires a linear relation between $a_{\text{H}_3\text{O}^+}$ and $a_{\text{H}_3\text{O}^+}/\text{slope}$. This linearity is found indeed. From the intercept another preliminary value for K_a of $3.4 \times 10^{-5} \text{ M}$ is found.

The linear dependence of k_1 on the acetic acid concentration in the right-hand side of the curves in Figure 4 cannot be distinguished kinetically from a linear dependence on the product of acetate and hydronium ion activities. However, the role of a second hydronium ion in the mechanism of this reaction will be difficult to explain. Therefore, in the subsequent discussion we prefer the linearity in acetic acid concentration. We conclude that product formation from protonated ynamine is assisted by acetic acid



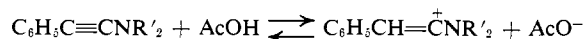
Extrapolation to zero acetic acid concentration of the straight lines in Figure 4 leads, amazingly, to nearly the same intercept. This intercept, which differs significantly from zero, can be understood if the conversion of the protonated ynamine into products also takes place with the assistance of hydroxyl ions instead of

acetic acid. In this case the straight line behavior can be expressed by eq 6

$$k_1 = \frac{a_{\text{H}_3\text{O}^+}}{K_a + a_{\text{H}_3\text{O}^+}}(k[\text{AcOH}] + k'a_{\text{OH}^-}) \quad (6)$$

with the intercept $k'a_{\text{H}_3\text{O}^+}a_{\text{OH}^-}/(K_a + a_{\text{H}_3\text{O}^+})$ being approximately constant if $K_a > a_{\text{H}_3\text{O}^+}$.

The graphs in Figure 4 suggest very fast reactions at zero acetic acid concentration and retardation of these reactions by relatively low concentrations of buffer. This behavior is in accordance with the remark made in the beginning of this section that the acid-catalyzed reaction is retarded in acetic acid. Since the concentration of protons was checked to be constant, this retardation must be caused by either acetic acid or acetate ions. The effect cannot be due to a shift of the protonation reaction



by acetate ions. The presence of this equilibrium would mean the reaction to be specific acid catalyzed and the rate independent of buffer concentration. Ultraviolet data suggest the effect to be due to interaction with acetic acid. A shift is observed in the wavelength of maximum absorption of 1-piperidino-2-phenylacetylene when acetic acid is present (Table IV). After correction

Table IV. Ultraviolet Absorption Maxima of 1-Piperidino-2-phenylacetylene

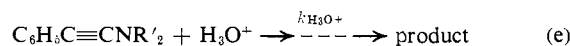
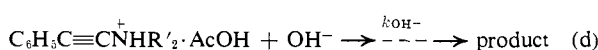
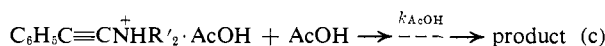
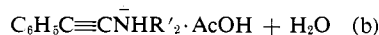
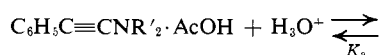
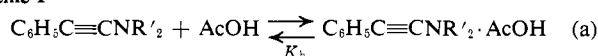
Solution ^a	λ_{max} , nm
0.183 M NaOH	282
0.005 M CH ₃ COOH + 0.015 M CH ₃ COONa ^b	298
0.05 M CH ₃ COOH + 0.02 M CH ₃ COONa ^b	298
0.05 M CH ₃ COONa	282
0.05 M CH ₃ COONa + 0.188 M NaOH	282

^a Solvent 8.6% v/v dioxane-water. ^b At different ionic strength.

for absorbance differences induced by the varying extent of protonation on nitrogen, only minor differences were found between the molar absorption coefficients in the basic and the acidic solutions. From the uv shift we suggest the retardation to be the result of complex formation between ynamine and acetic acid.

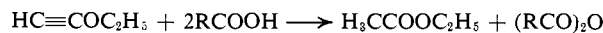
The more complete reaction mechanism is given in Scheme I. In this scheme reactions (e) and (f) describe

Scheme I

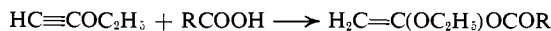


the general acid catalysis as outlined above for the basic medium. Catalysis by water is omitted because it will be small relative to the catalysis by acetic acid.

The involvement of a second molecule of acetic acid in step (c) of Scheme I has its analog in the literature, *viz.* in the formation of anhydrides in the reaction between ethoxyethyne and carboxylic acids in benzene, dioxane, sulfolane, and dimethylformamide as solvents.²¹ The first part of this reaction is the addition



of one molecule of carboxylic acid. The slow step of



the latter reaction is the transfer of a proton from carboxylic acid to acetylene. However, in the transition state of this slow step at least one more molecule of carboxylic acid is present.

The rate equation corresponding with Scheme I was derived assuming equilibria (a) and (b) to be fast relative to the product forming steps. The first-order rate constant is

$$k_1 = \frac{k_{\text{AcOH}}[\text{AcOH}]^2 a_{\text{H}_3\text{O}^+} + (k_{\text{OH}^-}K_w + k'_{\text{AcOH}}K_hK_a) \times [\text{AcOH}] + k_{\text{H}_3\text{O}^+}K_hK_a a_{\text{H}_3\text{O}^+}}{K_hK_a + K_a[\text{AcOH}] + a_{\text{H}_3\text{O}^+}[\text{AcOH}]} \quad (7)$$

where $K_w = a_{\text{H}_3\text{O}^+}a_{\text{OH}^-}$. The coefficients in this equation were obtained by regression analysis of the experimental results (see Table V). With the values obtained

Table V. Coefficients^a in Eq 7 for the Reaction of Three Ynamines C₆H₅C≡NCR'₂ with Water in Acetic Acid-Sodium Acetate Buffer Solutions

	R' ₂ =		
	(CH ₂) ₅	(CH ₃) ₂	(CH ₂) ₂ -O(CH ₂) ₂
$k_{\text{AcOH}}, M^{-1} \text{sec}^{-1}$	958	547	12.8
$k_{\text{OH}^-}K_w + k'_{\text{AcOH}}K_hK_a, M \text{sec}^{-1}$	5.14×10^{-4}		
$k_{\text{H}_3\text{O}^+}K_hK_a, M \text{sec}^{-1}$	217×10^{-3}		
K_hK_a, M^2	6.11×10^{-9}		
K_a, M	5.13×10^{-5}	1.24×10^{-5}	0.78×10^{-5}

^a It is difficult to estimate errors in the values obtained for the coefficients. From intermediate results during the computer search for the best fit of data it became clear that the possibility of cancelling between the various terms in eq 7 is certainly present. For instance, it was found that a two- to threefold change in some coefficients caused a change of 5% in the sum of the squared differences between the experimental and calculated first-order rate constants, $\sum(k_1^{\text{exptl}} - k_1^{\text{calcd}})^2$. The sum measures the "fit" of the data in eq 7. We therefore tend to believe that the real values of the coefficients lie between 1/3 and 3 times the values given in this table.

the first-order rate constants have been calculated according to eq 7. The relation between experimental and calculated rate constants is expressed by

$$k_1^{\text{exptl}} = (0.99 \pm 0.05)k_1^{\text{calcd}} + (0.2 \pm 0.8)$$

(correlation coefficient 0.96). Table V also contains k_{AcOH} and K_a values for two differently substituted ynamines. The remaining constants are omitted because the rate profiles of these ynamines were almost exclusively limited to the linear, the right-hand parts. The rate constant k_{AcOH} decreases with increasing electronegativity of the substituent indicating that the attack

(21) B. Zwanenburg and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **82**, 862, 879 (1963).

by acetic acid on the protonated ynamine is preponderantly electrophilic.

The K_a values in Table V express the acidity of the ynamine-acetic acid complex. The constants K_a can be obtained independently from spectrophotometric measurements because the absorbance decreases upon protonation. In this way for $R'_2 = (CH_2)_5$, $(CH_3)_2$, and $(CH_2CH_2)_2O$, $K_a \times 10^5$ is equal to 1.4, 2.8, and 2.2 M , respectively. Considering the inaccuracy of the data in Table V, both series of K_a do not differ significantly.

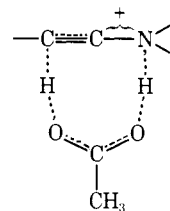
The pK_a values of about 5 are in the same order of magnitude as the estimate of $pK_a \leq 5.6$ obtained from eq 6. However, when comparing these pK_a values with those of other amines, it must be kept in mind first that our measurements were performed in 8.6 vol. % aqueous dioxane instead of pure water and second, and probably more important, that it is not the free ynamine that is protonated but the ynamine-acetic acid complex.

For the uncomplexed piperidino compound a value of $k_{H_3O^+} = 3.5 \times 10^7 M^{-1} sec^{-1}$ can be calculated from the data in Table V. In the most acidic solution of Table I this would correspond with a contribution to k_1 of 3 sec^{-1} . This contribution is too small to be detected in agreement with the experimental facts.

From the product $K_h K_a$ and the value for K_a it appears that K_h is approximately $10^{-4} M$ corresponding with a free energy of 4.5 ± 1.5 kcal/mol. Thus, the interaction between acetic acid and ynamine in aqueous solution is appreciable. In aqueous solution simple hydrogen bridge formation between acetic acid and the π system would be too weak to be detectable. The interaction seems to be more or less specific for ynamines because for phenylacetylenic ether we did not observe a shift in ultraviolet absorption maximum (246 nm) from neutral to basic and to aqueous acetic acid solution. The interaction might be a model for enzyme substrate cohesion.

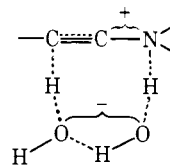
In Scheme I reactions (e) and (f) are extensions of the general acid catalysis picture in basic solution. Therefore, they probably also proceed through a vinyl cation intermediate. Reactions (c) and (d) of Scheme I give the same product, the amide, as reactions (e) and (f). Analogously, we presume that reactions (c) and (d) also proceed by slow formation of vinyl cations. This means that the catalytic action of acetic acid and of hydroxyl ions in these reactions in fact is an acceleration of the transformation of the protonated ynamine into the vinyl cation. This transformation consists of two operations, *viz.* removal of a proton from nitrogen and donation of a proton to the β -carbon atom. If the proton on nitrogen were to be removed before subsequent proton donation, the kinetics would change since the nonprotonated ynamine would be the substrate. Proton donation to the β -carbon atom before the proton on nitrogen is removed would give a doubly charged

cation which is energetically less favorable. A reasonable possibility seems to us a concerted process in which proton removal and donation occur in one step. Thus, the transition state of the slow step of reaction (c) would be a complex of



with CH_3COOH .

The hydroxyl ions operative in reaction (d) can give, in their hydrated form, a closely analogous proton transfer



in a complex with CH_3COOH .

Scale models show an almost perfect geometrical fit between protonated ynamine and acetic acid and between protonated ynamine and hydrated hydroxyl ion. This reaction is an example of bifunctional catalysis in aqueous solution. Bifunctional catalysis is catalysis by two catalytic entities present in one molecule. Bifunctional catalysis by molecules containing carboxyl and similar groups is known; however, the most illustrative examples appear to happen in aprotic solvents. Recent examples are given by, *e.g.*, Chuaqui, *et al.*,²² Ahlberg and Ladhar,²³ and Kepler, *et al.*²⁴ Reviews have been published by Bender,²⁵ Kaiser and Kézdy,²⁶ and Li.²⁷

Bifunctional catalysis is interesting because it is thought to be able to bridge classical catalysis and the much more efficient enzyme catalysis.²⁶

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