study and a more detailed analysis of the nortriquinacene system will appear elsewhere.
(50) This procedure was initially developed by Dr. James D. Kramer in these laboratories.
(51) R. C. Kelly, Ph.D. Thesis, Harvard University, 1965; R. Russo, Y. Lambert, and P. Deslongchamps, *Can. J. Chem.*, **49**, 531 (1971).

Catalysis of Transimination Through Trapping by Acids and Bases[1]

John L. Hogg, David A. Jencks, and William P. Jencks*

Contribution No. 1150 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. *Received December 27, 1976*

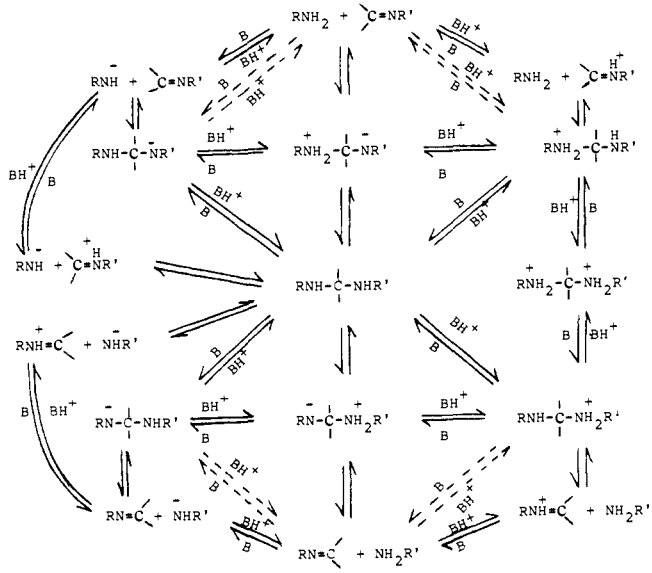
Abstract: Catalysis of the transimination reaction of *N*-*p*-methoxybenzylidenepyrrolidinium cation and hydroxylamine by buffer acids and bases and by the proton exhibits a sharp rate increase followed by a leveling off to a pH-independent rate at high catalyst concentrations. This is evidence for a change in rate-determining step and an intermediate in a stepwise reaction mechanism. Catalytic constants, k_{HA}, for cacodylic and carboxylic acids show a small or no increase with increasing acidity, but k_{HA} for the proton is 57 times larger and k_{HA} for hydroxylammonium ion is more than ten times smaller than k_{HA} for cacodylic and acetic acids. Catalytic constants for buffer bases drop sharply for catalysts of $pK_a < 4.6$. The reaction with *N*-methylhydroxylamine shows similar behavior in acetate buffers, but exhibits approximately tenfold slower rates, presumably because of steric hindrance. The observed catalysis by acids and bases is attributed to trapping of the initially formed cationic addition intermediate by proton transfer. Catalysis by cacodylic and carboxylic acids and by water is attributed to a bifunctional, proton switch mechanism.

Transimination (eq 1), such as occurs in the reaction of an amino acid with the imine formed from pyridoxal phosphate and the lysine ϵ-amino group of an enzyme, is an apparently

$$R_1NH_2 + \text{>C=NR}_2 \rightleftharpoons R_1N{=}C\text{<} + R_2NH_2 \quad (1)$$

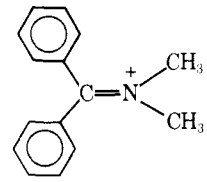
simple reaction that is made complicated by the requirement that two protons be removed from the attacking amine and added to the leaving amine. An oversimplified summary of the possible mechanisms for transimination, which omits all transport (diffusion) steps, is shown in Scheme I. Although the

Scheme I

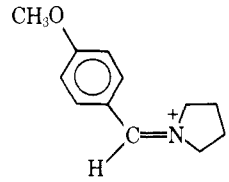


role of the gem diamine in the center of Scheme I as an intermediate has been questioned,[2] a recent temperature-jump study of the reaction of pyridoxal phosphate with ethylenediamine has not only identified this species, but has shown that it is formed rapidly enough to be kinetically competent as an intermediate in the nonenzymic transimination reaction and also in enzymic reactions, if the enzyme can bring together the reacting groups as effectively as in the model reaction.[3]

It was shown by Cordes and co-workers[4] that the transimination reaction of benzhydrylidenedimethylammonium ion (**1**) and hydroxylamine is subject to general base catalysis



1



2

according to the rate law

$$v = k_1[HONH_2][\text{>C=N}^+\text{<}] + k_B[HONH_2][\text{>C=N}^+\text{<}][B] \quad (2)$$

Some of the possible kinetically ambiguous mechanisms of catalysis in the upper right corner of Scheme I are eliminated by this result because the *N*-dimethyliminium ion is cationic initially, so that catalysis cannot involve the addition of a proton to the neutral imine. The experiments described here were initiated in an attempt to utilize the converse of this technique, in which a (fixed) methyl group serves as a model for a (mobile) proton. Catalysis of the reaction of **1** with hydroxylamine and with *N*-methylhydroxylamine was compared in an attempt to determine whether removal of the second proton from hydroxylamine in one of the steps shown in the lower half of Scheme I is involved in the catalysis. If this proton removal is important for the hydroxylamine reaction no such catalysis should be seen for the reaction with *N*-methylhydroxylamine, in which this proton removal is not possible. A series of preliminary experiments carried out by Moore and Reenstra showed that the terms k_1 and k_B in the rate law of eq 1 are 300 and 1600 times smaller, respectively, for the reaction of *N*-methylhydroxylamine than of hydroxylamine with **1**.[5] This result could be interpreted in terms of the catalytic mechanism or could simply reflect an unexpectedly large unfavorable steric effect from the methyl group of *N*-methylhydroxylamine.

The experiments described here were carried out with the less hindered cationic imine **2** in an attempt to distinguish between these interpretations. The results show that hydroxylamine and *N*-methylhydroxylamine both show the same type of catalysis, with only a ten-fold rate difference, indicating that a steric effect accounts for the observed rate difference in the reactions with **1**. This result, an observed change in rate-determining step with changing buffer concentration, and an approximate estimation of the relative catalytic effectiveness of different buffers serve to rule out several possible mechanisms and are consistent with the concurrent operation of several of the stepwise mechanisms of catalysis shown on the righthand side of Scheme I. Fox and Chalovich have independently obtained evidence for a stepwise mechanism of catalysis in the transimination of benzylideneanilines.[6]

Experimental Section

N-*p*-Methoxybenzylidenepyrrolidinium perchlorate (**2**) was prepared by the method of Leonard and Paukstelis.[7] The product had mp 117–118 °C, IR 1645 (>C=N$^+$<, in $CHCl_3$) or 1654 cm^{-1} (in Nujol),[8] UV λ_{max} 315 nm, ϵ 14 200. Methoxyacetic acid was redistilled; cacodylic acid, chloroacetic acid, hydroxylamine hydrochloride, and *N*-methylhydroxylamine hydrochloride were recrystallized before use. Other reagents were commercial preparations. Glass-distilled water was used throughout.

Reaction rates were measured spectrophotometrically by following the disappearance of the absorption of **2** at 315 nm. The reactions were initiated by the addition of 0.10 mL of a 7.5×10^{-4} M solution of the perchlorate salt of **2** in acetonitrile to 2.9 mL of buffer solution in a 1-cm cuvette that had been equilibrated in the thermostated cell compartment of a recording spectrophotometer. Rate constants were determined under pseudo-first-order conditions in the presence of a large excess of amine and pseudo-first-order rate constants were calculated from half-times that were obtained from semilogarithmic plots of $A_t - A_\infty$ against time. The absorbance change was accurately first order for at least two half-times except for the experiments with hydroxylamine at relatively high pH in cacodylate buffers. Because of the rapid rate of these reactions, only a sixfold excess of hydroxylamine was present and the rate constants were estimated from the initial slopes of the first-order plots; consequently, these rate constants are less accurate than those obtained at lower pH values. Apparent second-order rate constants, k', were obtained from the relation $k' = (k_{obsd} - k_w)/[\text{amine}]$; the first-order rate constant for hydrolysis, k_w was measured directly in the absence of amine at the same buffer concentration or was interpolated from plots of k_w against buffer concentration, and the concentration of amine free base was calculated from the total concentration of amine, the measured pH of a reaction mixture containing 0.067 M buffer, and pK_a values of 6.17 and 6.15 for hydroxylamine hydrochloride and *N*-methylhydroxylamine hydrochloride, respectively.[9]

All kinetic data, pH measurements, and pK values refer to solutions at ionic strength 1.0 M, maintained with potassium chloride. An increase in the observed pH of 0.20 ± 0.02 units was observed with the carboxylic acid buffers, 80% anion, when the buffer anion was substituted for chloride anion with increasing buffer concentration up to 1.0 M at ionic strength 1.0 M. No correction was made for this change in pH because a similar increase of 0.21 pH units was observed when 1 M potassium chloride was replaced by 1 M potassium methoxyacetate (previously adjusted to pH 6.0) in the presence of a 0.1 M hydroxylamine–hydroxylamine hydrochloride buffer at pH 6.08. This result shows that the apparent pH and pK of carboxylic acid and of hydroxylamine buffers are shifted in the same way when chloride is replaced by carboxylate anion, possibly because of an effect of this change on the glass electrode system used for pH measurement; any uncertainty introduced by this effect does not influence the catalytic constants in any case, because the catalytic constants were calculated from data obtained below 0.2 M buffer concentration, at which these salt effects are small. If the concentrations of hydroxylamine or *N*-methylhydroxylamine hydrochloride were large enough to affect the pH of the reaction mixtures, stock solutions were neutralized so as to give the same pH as low concentrations of buffer at ionic strength 1.0 M before each experiment. In order to correct for variations in hydroxylamine concentration and measured pH values (to which the calculated rate constants are very sensitive) in experiments carried out on different days, most of the rate constants that were used for the calculation of catalytic constants were normalized to the values obtained in a single experiment in which rate constants for the hydroxylamine reaction were determined in 1 M solutions of the same buffer solutions that were used for the individual experiments.

Kinetic Equations. For a reaction with a catalyzed step and one or more uncatalyzed steps, such as eq 7 in the Discussion section, the observed second-order rate constant k' in the presence of a given concentration of catalyst and under steady-state conditions is given by

$$k' = \frac{k_1 k_c / k_{-1}}{k_c/k_{-1} + k_{-c}/k_2 + 1} \tag{3}$$

in which $k_c = k_h + k_c'$ [catalyst]; $k_{-c} = k_{-h} + k_{-c}'$ [catalyst]; k_h and k_{-h} represent catalysis by water. In order to determine catalytic constants it is necessary to calculate what the observed rate constant, k', would be if the catalyzed step were entirely rate determining and other steps were fast. This rate constant, k_{corr}, is related to k_c by the equilibrium constant for the formation of the addition intermediate, k_1/k_{-1}.

$$k_{corr} = (k_1/k_{-1})k_c = k_0 + k_{cat}[\text{catalyst}] \tag{4}$$

The value of k_{corr} was obtained from eq 5, in which k_∞ is the limiting rate constant at infinite catalyst concentration. Equation 5 was obtained from eq 3 and 6;

$$k_{corr} = k'/[1 - (k'/k_\infty)] \tag{5}$$

$$k_\infty = \frac{k_1 k_c / k_{-1}}{k_c/k_{-1} + k_{-c}/k_2} = \frac{k_{corr}}{k_c/k_{-1} + k_{-c}/k_2} \tag{6}$$

eq 6 describes the rate under conditions in which the proton-transfer steps are fast. Values of k_∞ were obtained from the limiting observed second-order rate constants at low pH for the hydroxylamine reaction and from an extrapolation of observed rate constants to infinite buffer concentration with a Hofstee–Eadie type plot of k' against $(k' - k_0')/[\text{buffer}]$ for the *N*-methylhydroxylamine reaction; k_0' is the observed rate constant extrapolated to zero buffer concentration. It can be shown that the ratio of $(k' - k_\infty)$ to $(k' - k_0')/[\text{buffer}]$ is constant by calculating these terms from eq 3 and the definitions of k_c and k_{-c}; therefore, this plot is linear with ordinate intercept k_∞.

Results

The transimination reaction of hydroxylamine with **2** to form *p*-anisaldehyde oxime is strongly catalyzed by acetate buffers at low buffer concentrations, but exhibits a leveling off and shows little or no catalysis at high buffer concentration. The results for 20 and 80% ionized acetate buffers, expressed as apparent second-order rate constants based on the concentration of hydroxylamine free base, are shown in curves 1 and 2 of Figure 1, respectively. The following results were obtained and are illustrated by representative data in Figure 1:

(a) The catalysis observed with acetate buffers that contain 20 and 80% acetate anion is comparable (curves 1 and 2), suggesting that both acetic acid and acetate anion are active as catalysts.

(b) Catalysis by 20% ionized cacodylic acid buffers (curve 3) is very similar to that by acetic acid buffers, suggesting that the catalytic constants for cacodylic and acetic acids are similar in spite of the 30-fold smaller acidity of cacodylic acid.

(c) Catalysis by 20% ionized methoxyacetate (curve 4) and chloroacetate (curve 5) buffers is less marked because the rate constants in the absence of buffer are higher at the lower pH values of these buffers. This indicates that hydrogen ion is also a catalyst and that when the rate is increased by hydrogen ion catalysis a correspondingly smaller additional rate increase can be brought about by buffer catalysis.

(d) The rate constants appear to approach similar, but not identical, limiting values near 600 M^{-1} s^{-1} at high buffer concentrations. The absence of a significant trend in the limiting rate constants over a pH range of 0.25–7.0 shows that there is no significant hydrogen or hydroxide ion catalysis of the limiting rate over this range of pH.

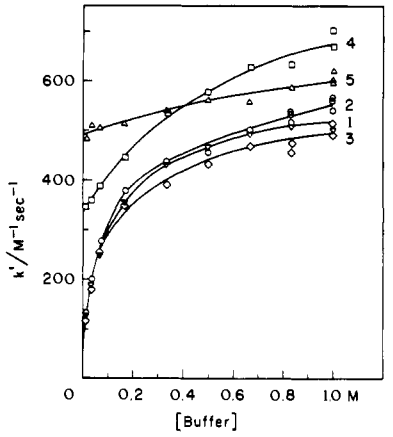


Figure 1. Catalysis of the reaction of hydroxylamine with **2** at 25 °C, ionic strength 1.0 M (KCl): Curves 1 and 2, acetate buffers, 20 and 80% ionized, respectively; curve 3, cacodylic acid buffer, 20% ionized; curve 4, methoxyacetate buffer, 20% ionized; curve 5, chloroacetate buffer, 20% ionized.

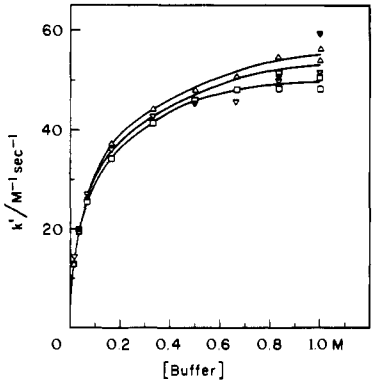


Figure 2. Catalysis of the reaction of *N*-methylhydroxylamine with **2** by acetate buffers, 20 (▽), 50 (□), and 80% (△) ionized, at 25 °C, ionic strength 1.0 M (KCl).

(e) The shape of the curves for the 20% ionized buffers is that expected for a change from a buffer-catalyzed to an uncatalyzed rate-determining step with increasing buffer concentration and plots of k' against $(k' - k_0')/[\text{buffer}]$ are linear for these buffers, as expected for such a mechanism. However, similar plots for the 50 and 80% ionized buffers exhibit positive deviations from linearity at high buffer concentrations and a continued small increase in rate at high buffer concentrations is apparent for the 80% ionized acetate buffers in Figure 1 (compare curve 2 with curve 1). This increase probably represents a specific salt effect caused by the substitution of carboxylate for chloride ion as the buffer concentration is increased at an ionic strength maintained at 1.0 M by potassium chloride. Such an effect has been observed for the uncatalyzed and the acetate-catalyzed hydrolysis of **2** in acetate buffers and is caused by an inhibitory effect of potassium chloride on the rate that is relieved when carboxylate ion is substituted for chloride ion.[10] Although a detailed study of specific salt effects on the hydroxylamine reaction has not been carried out, the hydroxylamine and hydrolysis reactions both involve the addition of an uncharged nucleophile to **2** and a 10–20% rate increase was observed for the hydroxylamine reaction when 0.6 M potassium chloride was omitted from reaction mixtures containing 0.5–0.6 M cacodylate buffers (0.4 M anion). Since the magnitude of the specific salt effect that is required to account for the observed increase at high buffer concentrations is less than half of that which was observed for the hydrolysis reactions,[10] this increase cannot be taken as evidence for buffer catalysis of the limiting rate and may reasonably be attributed to a specific salt effect. The salt effect also provides an explanation for the variation in the limiting rate constants in the different buffer solutions. Because of the uncertainties introduced by this specific salt effect, rate constants obtained at buffer concentrations of over 0.2 M were not used for the calculation of catalytic constants.

Catalysis by acetate buffers of the transimination of **2** with *N*-methylhydroxylamine (Figure 2) exhibits almost identical behavior with that with hydroxylamine, except that the rate constants are an order of magnitude smaller. Again, the similar behavior of 20, 50, and 80% ionized buffers indicates that both acetic acid and acetate ion are effective catalysts.

The slower rate of reaction of the *N*-methyl compound is attributed to an unfavorable steric effect of the methyl group because of the much larger rate decrease, of 300-fold for the uncatalyzed reaction, and 1600-fold for the catalyzed reaction, that was observed for *N*-methylhydroxylamine compared with hydroxylamine in the reaction with **1**.[4] Although it appeared initially that this might represent a different mechanism of catalysis for the two amines, the smaller rate difference with the less hindered imine **2** suggests that it simply represents a steric effect.

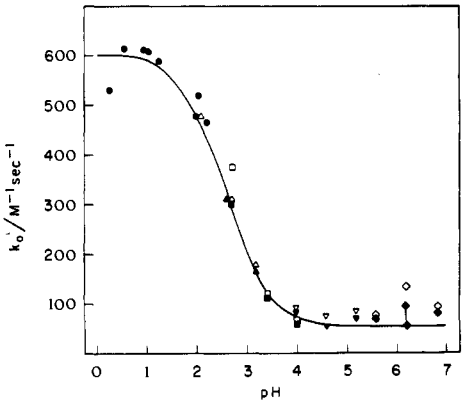


Figure 3. Dependence on pH of the buffer-independent reaction of hydroxylamine with **2** at 25 °C, ionic strength 1.0 M (KCl): Closed circles, pH maintained with hydrochloric acid; open symbols, rate constants extrapolated to zero concentration of chloroacetate (△), methoxyacetate (□), acetate (▽), and cacodylate (◇) buffers. The rate constants indicated by the other closed symbols were obtained as described in the text. The solid line is calculated from the rate constants in Table II.

The dependence on pH of the reaction of hydroxylamine with **2** at zero buffer concentration follows a sigmoid curve, as shown in Figure 3. The open symbols represent extrapolations to zero buffer concentration of data similar to that shown in Figure 1 and are of low accuracy because of the large slope and nonlinearity of the plots. The solid symbols for the buffer experiments were obtained from the corrected rate constants for buffer catalysis (k_{corr}, extrapolated to zero buffer concentration), as described below, which were converted to observed rate constants (k') by eq 5. The solid circles represent rate constants obtained in hydrochloric acid solutions. Figure 3 shows that the buffer-independent rate represents a pH-independent, "water" reaction above pH 5, a proton-catalyzed reaction below pH 4, and a leveling off to a limiting rate constant of 600 M^{-1} s^{-1} at pH 1. Since specific salt effects should be negligible for the experiments carried out in dilute hydrochloric acid solution (because there is no change in the anion and only a very small change in the cation at low acid concentrations), this value of 600 M^{-1} s^{-1} is taken as the limiting rate constant, k_∞, for the uncatalyzed reaction. The leveling off of the rate at low pH confirms the conclusion obtained from the buffer experiments that this limiting rate is itself not subject to catalysis.

Table I. Catalytic Constants for Carboxylic and Cacodylic Acid Buffers in the Reactions of Hydroxylamine and *N*-Methylhydroxylamine with **1** at 25 °C, Ionic Strength 1.0 M (KCl)

Buffer	% ionized	$10^{-3}\,k_{cat}$, $M^{-2}\,s^{-1}$
	Hydroxylamine	
Chloroacetic acid	20	7[a]
	50	5.9[a]
	80	2.2
Methoxyacetic acid	20	6.1[a]
	50	3.2
	80	2.1
Acetic acid	20	5.0
	50	7.8
	80	8.6
Cacodylic acid	20	6.0
	50	10.7
	80	17 ± 4
	N-Methylhydroxylamine	
Acetic acid	20	0.64
	50	0.59
	80	0.59

[a] Approximate value because of interference from catalysis by hydrogen ion.

Catalytic constants for the buffer-catalyzed step were obtained by correcting the individual rate constants for the contribution of the uncatalyzed step using eq 5 and a value of $k_\infty = 600\ M^{-1}\,s^{-1}$. Plots of the corrected rate constants, k_{corr}, against buffer concentration in the range 0–0.067 or 0.133 M were linear and gave slopes, k_{cat}, that are summarized in Table I. The results from the more acidic chloroacetic and methoxyacetic acid buffers are of low reliability because of the small rate increase that results from competing catalysis by the proton (Figure 1, curves 4 and 5). The catalytic constant for the proton was estimated by the same procedure, based on the data in Figure 3 that were obtained at low concentrations of hydroxylammonium ion. All of the data were found to be consistent with this value after correction for catalysis by hydroxylammonium ion (see below). Values of k_{cat} for the *N*-methylhydroxylamine reaction in acetate buffers were calculated similarly and are also given in Table I. A value of 55 ± 3 $M^{-1}\,s^{-1}$ for the limiting, buffer-independent rate constant of the *N*-methylhydroxylamine reaction was obtained from the ordinate intercepts of plots of k' against $(k' - k_0')/[\text{buffer}]$ for the three acetate buffers.

Catalytic constants for the acidic and basic species of the buffers were obtained from the intercepts of plots of k_{cat} against the fraction of anion in the buffer and are summarized in Table II. These catalytic constants are not of high precision because of the correction for the change in rate-determining step, but they do serve to indicate the approximate relative effectiveness of the different catalysts.

An attempt was made to determine the catalytic constant for hydroxylammonium ion by measuring the rate at total hydroxylamine concentrations up to 0.5 M in the presence of 0.001 M hydrochloric acid (Figure 4, lower line). Catalysis of the reaction of hydroxylamine by hydroxylammonium ion would give a second-order dependence of the observed rate constants on total hydroxylamine concentration and an upward curvature in a plot against hydroxylammonium ion concentration. A small upward curvature is evident in the plot (Figure 4), but is insufficient to establish definitely the existence of catalysis by hydroxylammonium ion. The observed pH was found to decrease by 0.1 unit with increasing hydroxylammonium chloride concentration and a plot of k' (based on the concentration of hydroxylamine as the free base) against hydroxylammonium ion concentration shows a small slope (upper line, Figure 4). After correction for the contribution of the uncatalyzed step and for catalysis by hydrogen ion, a catalytic constant of 380 $M^{-2}\,s^{-1}$ was obtained for hydroxylammonium ion. This can only be regarded as an upper limit for the true catalytic constant in view of the small magnitude of the observed catalysis; in any case it is smaller than the catalytic constants for any of the other acid catalysts examined by more than an order of magnitude. Under the same conditions low concentrations of cacodylic acid, which has approximately the same acidity as hydroxylammonium ion, give much larger catalysis (triangles, Figure 4). A catalytic constant of 4300 ± 300 $M^{-2}\,s^{-1}$ for cacodylic acid was calculated from these data and agrees with the value obtained from the experiments with cacodylic acid buffers (Table I).

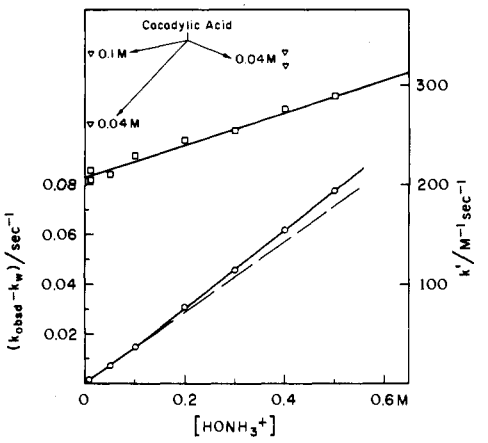


Figure 4. Dependence on hydroxylammonium ion concentration of the first-order (lower curve, left ordinate) and second-order (upper curve, right ordinate) rate constants for the reaction of **2** with hydroxylamine in the presence of 0.001 M hydrochloric acid at 25 °C, ionic strength 1.0 M (KCl): triangles, cacodylic acid added at the indicated concentrations.

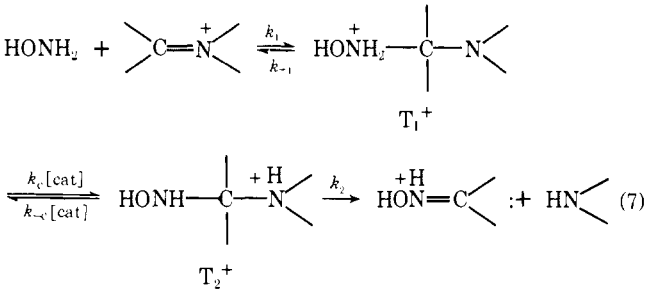
Table II. Catalysis of the Reaction of Hydroxylamine and *N*-Methylhydroxylamine with **2** by Acids, k_{HA}, and Bases, k_{A^-}, at 25 °C, Ionic Strength 1.0 M (KCl)

Catalyst (acidic species)	pK_a	$10^{-3}\,k_{HA}$, $M^{-2}\,s^{-1}$		$10^{-3}\,k_{A^-}$, $M^{-2}\,s^{-1}$
	Hydroxylamine			
H^+	−1.74	250		
Chloroacetic acid	2.70[a]	10[b]		≤1.0
Methoxyacetic acid	3.40[a]	7.0[b]		≤1.0
Acetic acid	4.65[a]	4.4		10.3
Cacodylic acid	6.15[c]	4.3		15
Hydroxylammonium ion	6.17[d]	≤0.38		
Water	15.74		60[e]	
			1.1[f]	
	N-Methylhydroxylamine			
Acetic acid	4.65	0.62		0.59
Water	15.74		9.8[e]	
			0.18[f]	

[a] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6353 (1969). [b] Approximate value. [c] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 5637 (1973). [d] Reference 9. [e] Second-order constant, $k_0'/M^{-1}\,s^{-1}$. [f] Third-order constant = $k_0'/55.5$.

Discussion

The following evidence is consistent with the stepwise mechanism of eq 7 for the transimination of **2** with hydroxylamine and with *N*-methylhydroxylamine. Two proton transfers (k_c) are required to convert the initially formed cationic addition compound T_1^+ to T_2^+, which can break down to give products. According to this mechanism the observed buffer catalysis represents facilitation by acids and bases of these proton-transfer steps, which are also mediated by solvent. The proton-transfer steps occur at a rate which approaches the diffusion-controlled limit with the most effective catalysts. When the buffer concentration is increased sufficiently so that the proton-transfer steps are fast, the uncatalyzed attack or expulsion of amine becomes rate determining and buffer catalysis is no longer observed.



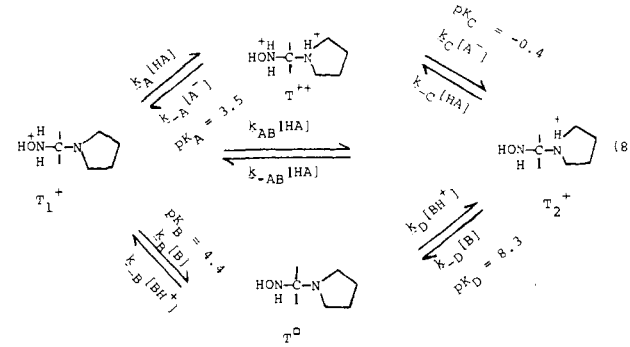
(7)

(1) There is a change in rate-determining step with increasing buffer or hydrogen ion concentration from a step which is strongly catalyzed to one which shows no evidence for catalysis (Figures 1-3). This requires that there be an intermediate and at least two steps in the reaction, consistent with the mechanism of eq 7. The limiting rate constant at high buffer or proton concentration, when k_1 and/or k_2 becomes rate determining, is the same for all catalysts from pH 0.25 to 7.0 within the limits expected from experimental error and specific salt effects; in particular, it is constant over a fivefold range of proton concentration from 0.05 to 0.25 M.

(2) The maximum rate constants for catalysis by buffer acids and bases are similar both for the hydroxylamine and for the *N*-methylhydroxylamine reactions (Table II), as would be expected if the rate of the proton-transfer step approaches the diffusion-controlled limit with the most effective catalysts.

(3) The rate constants for catalysis by carboxylic and cacodylic acids differ by a factor of <3 over a range of acid strength of more than 10^3 and the proton is between one and two orders of magnitude more effective as a catalyst (Table II). The finding of a small or no dependence on acid strength and an increased rate constant for the proton, which is capable of facilitated diffusion, is expected for a mechanism of catalysis that involves trapping an unstable intermediate upon encounter with an acid at a rate that approaches the diffusion-controlled limit.[11]

(4) In contrast to the behavior of acids, the catalytic efficiency of carboxylate and cacodylate anions is sensitive to their pK and drops off sharply for bases of pK < 4.6 (Table II). This is the behavior that is expected if catalysis by strong bases involves a diffusion-controlled trapping of the intermediate, possibly facilitated by a favorable electrostatic interaction between T_1^+ and the buffer anion, whereas proton transfer becomes thermodyamically unfavorable with weak bases so that the rates of proton transfer and catalysis decrease. The pK_a values of the addition intermediate (eq 8) were estimated by the method described previously,[12] based on pK_a values of 5.96 for *N*-methylhydroxylammonium ion and 10.46 for *N*-methylpyrrolidinium ion;[13] a contribution of 0.13 pK units was allowed for the effect of the *p*-methoxy substituent on the benzene ring, based on the difference in pK of benzylammonium and *p*-methoxybenzylammonium ions.[14] The calculated pK_a value of 4.4 for dissociation of the hydroxylammonium group in T_1^+ is consistent with the decreased catalytic constants for bases of pK_a < 4.6. The other calculated pK_a values for the intermediate are shown in eq 8.

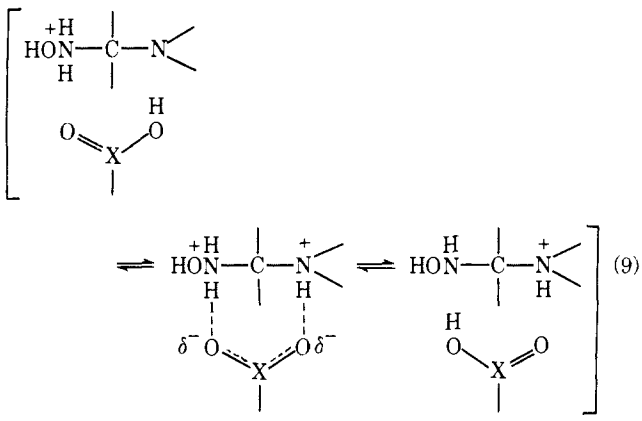


(8)

(5) A mechanism of general-acid catalysis that involves assistance to the attack or departure of amine by hydrogen bonding or concerted catalysis is improbable because there is no basic site for such catalysis in a cationic imine. Catalysis of amine attack would require hydrogen bonding or proton donation to a cationic imine (**2**) and the microscopic reverse of such catalysis, in the expulsion of pyrrolidine, cannot involve hydrogen bonding or proton removal by A^- from T_2^+, because catalysis is also observed in the *N*-methylhydroxylamine reaction, for which such catalysis is impossible. However, acid catalysis that involves trapping of the intermediate T_1^+ is reasonable, because a basic site for protonation develops on the pyrrolidine nitrogen atom when this intermediate is formed.

(6) Significant catalysis by acids of pK_a > 3.5 through a concerted or hydrogen bonding mechanism is excluded by a rule that states that proton transfer between the catalyst and product must become thermodynamically favorable in order that such catalysis can occur.[15] Acid catalysis by a weak acid in the forward direction corresponds to base catalysis by a strong base in the reverse direction and, so long as the intermediate T_1^+ has a significant lifetime, the reaction of T^{2+} with a strong base would lead to a diffusion-controlled proton transfer, followed by breakdown of T_1^+ in a subsequent slow step, rather than to a concerted breakdown.[15] Catalysis by hydrogen bonding to weak acids is unlikely because hydrogen bonds between a weak acid and a weak base do not provide a signficant thermodynamic advantage in water and the basicity of the pyrrolidine nitrogen atom in the transition state is expected to be even lower than in T_1^+.

Cacodylic and acetic acids are only slightly less effective catalysts than methoxyacetic and chloroacetic acids, although proton transfer from the former acids to the pyrrolidine nitrogen atom of the addition intermediate is thermodynamically unfavorable (the estimated pK of this group in T^{2+} is 3.5 [eq 8]), so that proton transfer from these relatively weak acids would be expected to occur at a rate that is much less than diffusion controlled.[11] Furthermore, hydroxylammonium ion (pK_a = 6.17) is more than an order of magnitude less effective than cacodylic acid (pK_a = 6.15) as an acid catalyst (Table II). This difference is larger than would be expected for an electrostatic effect at ionic strength 1.0 and the solvated proton, which is also cationic but is a strong acid, is a very effective catalyst. The unexpectedly high reactivity of acetic and cacodylic acids suggests that these catalysts can trap the intermediate through a bifunctional mechanism of proton transfer in a single encounter with T_1^+ (eq 9). Bifunctional catalysis through a proton-switch mechanism of this kind is presumably also responsible for the "water" reaction, k_0, in the absence of added buffers. Bifunctional catalysis has been observed in several stepwise reactions;[16] it becomes significant only when the rate-determining proton transfer becomes thermodynamically unfavorable, because stronger acids will



(9)

react at a diffusion-controlled rate regardless of whether they are bifunctional or not.

The enhanced effectiveness of bifunctional catalysts suggests that the lowest energy pathway for proton tranfer in this and other reactions for which bifunctional catalysis has been observed is directly between the catalyst and the two sites in the unstable intermediate; if proton transfer occurred through an intermediate water molecule(s) a second proton transfer back through the water molecule at the other site should frequently result in trapping of the intermediate during a single encounter even with monofunctional catalysts such as the hydroxylammonium ion.[17] The proton transfer itself could occur either through the stepwise mechanism shown in eq 9 or through a concerted mechanism. A step involving the proton transfer itself and associated solvation changes is believed to become partially rate determining for simple proton-transfer reactions in the region of $\Delta pK \sim 0$[11] and, since catalysis by bifunctional catalysts does not become slow in the region of $\Delta pK \sim 0$, this catalysis presumably occurs through a concerted mechanism or with extra stabilization of the transition state for proton transfer by hydrogen bonding.

There is evidence that the lone pair electrons on one nitrogen atom should be *antiperiplanar* to the other nitrogen atom to provide the lowest energy transition state for amine expulsion; the transition state for attack must have the same geometry.[18] However, the cyclic transition state for proton transfer that is required for bifunctional catalysis (eq 9) is not compatible with this *antiperiplanar* geometry. The occurrence of bifunctional catalysis therefore provides evidence that inversion or rotation of nitrogen occurs rapidly after amine attack in order that the cyclic transition state may be formed. This inversion or rotation must be fast relative to trapping by proton transfer, which occurs at a close to diffusion-controlled rate, because the trapping step (k_c) is rate determining at low catalyst concentrations. Inversion or rotation does not become the rate-determining step at high concentrations of bifunctional catalysts because the same limiting rate constant and rate-determining step is reached at high concentrations of monofunctional acids and bases, which do not have the same stereochemical requirements as bifunctional catalysts. Inspection of molecular models suggests that hydroxylamine can attack the imine to give a conformation that can go on to products directly after proton transfer, without the rotation or inversion step that is required for bifunctional catalysts. Furthermore, it is unlikely that rotation and inversion could be slow enough to account for the values of k_{-1} and k_2 that are required by the data (see below).

The detailed mechanism of the proton-transfer steps, which are incorporated into the term k_c in eq 7, may be summarized as follows with reference to eq 8. The required proton transfers for the conversion of T_1^+ to T_2^+ may occur by acid catalysis with the intermediate formation of T^{2+} (upper path, eq 8), by base catalysis with the intermediate formation of T^0 (lower path, eq 8), or directly by bifunctional catalysis (center path, eq 8). The initial protonation, k_A, will be largely or entirely rate determining for the acid-catalyzed pathway because T^{2+} will generally lose its most acidic proton ($k_C[A^-]$) to give T_2^+ faster than it will revert to T_1^+ ($k_{-A}[A^-]$). The initial deprotonation, k_B, will be largely or entirely rate determining for the base-catalyzed pathway because T^0 will generally add a proton to its more basic nitrogen atom ($k_D[BH^+]$) to give T_2^+ faster than it will revert to T_1^+ ($k_{-B}[BH^+]$). If the bifunctional pathway, k_{AB}, itself proceeds through two steps within the encounter complex (eq 9), the first of these steps is expected to be slower, as in the case of the k_A pathway. These considerations lead to the generalization that for catalysis in a stepwise mechanism of transimination, the proton-transfer steps that are immediately adjacent (in time) to the attack or expulsion of the less basic amine molecule will be rate determining.

Quantitative and Structure–Reactivity Considerations. If it is assumed that the addition intermediate is trapped upon encountering a solvated proton with a diffusion-controlled rate constant[11] of 2×10^{10} M^{-1} s^{-1}, then the values of k_c' for other catalysts are 3.5×10^8 M^{-1} s^{-1} for acetic and cacodylic acids, $(1.0 \pm 0.2) \times 10^9$ M^{-1} s^{-1} for acetate and cacodylate anions, $\leq 3 \times 10^7$ M^{-1} s^{-1} for hydroxylammonium ion, and 4.8×10^6 s^{-1} for the proton switch through water. These values are consistent with the mechanisms of eq 7–9 and known rates of proton transfer.[11,19] A proton switch in a one-encounter mechanism avoids the diffusional separation of the products that is rate determining in ordinary thermodynamically unfavorable proton transfers, and shows a small increase in rate with increasing acidity when proton donation is dominant; when proton transfer becomes strongly unfavorable, as in the case of water, the proton switch occurs with a rate constant in the range of 10^6–10^8 s^{-1}.[19]

At the midpoint of the change in rate-determining step at pH 2.7 (Figure 3) the protonation and heavy-atom reorganization steps are equally rate determining. If the latter step involves amine attack the rate constant k_{-1} is then $10^{-2.7} \times 2 \times 10^{10} = 4 \times 10^7$ s^{-1}; if it involves pyrrolidine expulsion k_{-1} must be larger than this. If pyrrolidine expulsion becomes rate determining at high buffer concentration the value of k_2 is 5×10^3 s^{-1}; if k_1 is rate determining k_2 must be larger than this value.[20] The equilibrium constant for the formation of T_1^+ from reactants is given by $K_1 = k_{H^+}(obsd)/k_c' = 2.5 \times 10^5/2 \times 10^{10} = 1.3 \times 10^{-5}$ M^{-1}.

It is probable, but not proved, that it is the k_1 rather than the k_2 step that becomes rate determining at high catalyst concentrations. When proton transfer is at equilibrium, the pK_a values of eq 8 require that the concentration of T_2^+ will be $10^{3.9}$ higher than T_1^+, but it is not known whether this high concentration is enough to overcome the lower reactivity of T_2^+ for amine expulsion ($k_2 \geq 5 \times 10^3$ s^{-1}) compared with T_1^+ ($k_{-1} \geq 4 \times 10^7$ s^{-1}). It has been shown directly that attack and expulsion of the less basic aniline is rate determining in the transimination of benzylideneanilines[21] and there are a number of reactions in which protonation and expulsion of the more basic of two possible amine leaving groups is preferred.[22,23] However, the reduction of a model compound for methylenetetrahydrofolic acid gives a product with the methyl group on the more basic nitrogen atom, which suggests that the product of the equilibrium and rate constants are more favorable for reduction of the iminium compound that is formed with the more basic nitrogen atom.[24]

Catalysis of the reaction of **1** with hydroxylamine by formate buffer, 80% ionized, was found[25] to show curvature at buffer concentrations above 1 M that may represent an incipient leveling off and change in rate-determining step, but this occurs at much higher buffer concentrations than in the reactions of **2**. This is the behavior that is expected if the value of k_{-1} in the

reaction of **1** is larger than that with **2** because of crowding in the addition compound T_1^+ formed from **1**; if k_{-1} is larger, a higher concentration of catalyst must be added before the proton-transfer step, k_{cat}, is no longer rate determining.

A larger value of k_{-1} is also expected if there is more effective electron donation to expel the attacking amine. This has been observed by Benkovic and co-workers for the methoxyaminolysis of an amidine, which exhibits a nonlinear Brønsted plot for general-base catalysis that provides evidence for a stepwise mechanism with rate-determining proton transfer.[23] Since there are two nitrogen atoms in the tetrahedral addition compound to provide the driving force for the expulsion of the attacking amine and formation of the resonance-stabilized amidinium ion, the rate constant k_{-1} is considerably larger ($k_{-1} > 10^9$ M^{-1} s^{-1}, with no evidence for a change in rate-determining step up to 0.16 M phosphate buffer, 80% dianion) and K_1 is considerably smaller ($K_1 = 3.7 \times 10^{-13}$ M^{-1}) than for the transimination of **2**. On the other hand, no general-base catalysis by methoxyamine has been observed for the methoxyaminolysis of N-protonated benzylideneanilines.[26] The value of k_{-1} is expected to be smaller for this reaction because of the relatively small electron-donating ability of the aniline nitrogen atom. The absence of catalysis may therefore reflect a solvent-mediated proton transfer that is faster than k_{-1}, so that buffer-mediated trapping is not significant.

References and Notes

(1) Supported by grants from the National Science Foundation (BMS71-01501 A03) and the National Institute of General Medical Sciences of the National Institutes of Health (GM 20888).
(2) E. H. Abbott and A. E. Martell, *J. Am. Chem. Soc.*, **93**, 5852 (1971).
(3) P. S. Tobias and R. G. Kallen, *J. Am. Chem. Soc.*, **97**, 6530 (1975).
(4) K. Koehler, W. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, **86**, 2413 (1964).
(5) S. Moore and W. Reenstra, unpublished experiments.
(6) J. P. Fox and J. M. Chalovich, personal cummunication.
(7) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).
(8) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).
(9) J. E. Reimann and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3973 (1966).
(10) J. L. Hogg and W. P. Jencks, *J. Am. Chem. Soc.*, **98**, 5643 (1976).
(11) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(12) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 5637 (1973); J. P. Fox and W. P. Jencks, *ibid.*, **96**, 1436 (1974).
(13) W. P. Jencks and J. Regenstein, "Handbook of Biochemistry", 2nd ed, H. A. Sober, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970, p J-150.
(14) L. F. Blackwell, A. Fischer, I. J. Miller, R. D. Topsom, and J. Vaughan, *J. Chem. Soc.*, 3588 (1964).
(15) W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 4731 (1972).
(16) B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, **88**, 551 (1966); R. K. Chaturvedi and G. L. Schmir, *ibid.*, **90**, 4413 (1968); T. Okuyama, T. C. Pletcher, D. J. Sahn, and G. L. Schmir, *ibid.*, **95**, 1253 (1973); T. Okuyama, D. J. Sahn, and G. L. Schmir, *ibid.*, **95**, 2345 (1973); R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358 (1969).
(17) M. Eigen, *Discuss. Faraday Soc.*, **39**, 7 (1965).
(18) P. Deslongchamps, *Tetrahedron*, **31**, 2463 (1975).
(19) E. Grunwald, P. J. Karabatsos, R. A. Kromhont, and E. L. Purlee, *J. Chem. Phys.*, **33**, 556 (1960); E. Grunwald and S. Meiboom, *J. Am. Chem. Soc.*, **85**, 2047 (1963); D. D. Eley, A. S. Fawcett, and M. J. Hey, *J. Chem. Soc., Faraday Trans. 1*, 399 (1973); J. Hine, *J. Am. Chem. Soc.*, **94**, 5766 (1972); E. Grunwald, *Prog. Phys. Org. Chem.*, **3**, 317 (1965); S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7986 (1974).
(20) When proton transfer is half rate determining the rates of the forward and back reactions are equal, i.e., $k_{-c}[H^+] = k_2$ in eq 7. Since $k_{-c} = k_c K_A / K_C = 2 \times 10^{10} \times 10^{-3.5} / 10^{0.4} = 2.5 \times 10^6$ M^{-1} s^{-1} (K_A and K_C are defined in eq 8), $k_2 = 10^{-2.7} \times 2.5 \times 10^6 = 5 \times 10^3$ s^{-1}.
(21) J. P. Fox and W. P. Jencks, in preparation.
(22) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, pp 542–548; S. J. Benkovic, T. H. Barrows, and P. R. Farina, *J. Am. Chem. Soc.*, **95**, 8414 (1973).
(23) W. P. Bullard, L. J. Farina, P. R. Farina, and S. J. Benkovic, *J. Am. Chem. Soc.*, **96**, 7295 (1974).
(24) T. H. Barrows, P. R. Farina, R. L. Chrzanowski, P. A. Benkovic, and S. J. Benkovic, *J. Am. Chem. Soc.*, **98**, 3678 (1976).
(25) E. S. Hand, unpublished experiments.
(26) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, **88**, 2225 (1966).

A Method of Synthesis of β-Methylfurans and α-Methylene and β-Methylene γ-Lactones. Two Menthofuran Syntheses[1]

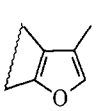
Ernest Wenkert,*[2] Miguel E. Alonso,[3] Brian L. Buckwalter, and Kechia Joseph Chou

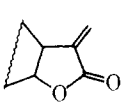
Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401.

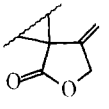
Received December 10, 1976

Abstract: The copper-catalyzed thermolysis of α-diazo-β-dicarbonyl compounds, diazoacetylacetone, methyl diazoacetoacetate, and dimethyl diazomalonate, in the presence of enol ethers of an aldehyde and a ketone is described. The first two diazo compounds produce 5-alkoxy-3-acyl-4,5-dihydrofurans, while diazomalonic ester is transformed into a cyclopropane derivative with the first enol ether and into an olefinic equivalent with the second enol derivative. The diazomalonate-derived products are convertible into β-methylfurans or their methylene lactone equivalents by simple reduction, oxidation, and isomerization operations. A method for the regioselective synthesis of one enol ether of β-methylcyclohexanone is introduced and the product converted into menthofuran by the above diazomalonate-initiated scheme as well as by a photolysis of methyl α-diazopropionate in its presence, followed by reduction, oxidation, and acid-induced dealcoholation.

As part of an ongoing program of study of the use of β-oxycyclopropylcarbonyl compounds, prepared by the interaction of diazomethyl ketones and carboxylates with enol ethers or esters, in organic synthesis,[4-6] especially directed toward terpenic natural products,[7] an investigation of the chemistry of functionally more complex α-diazoketo systems was initiated.[8] The present paper deals with α-diazo-β-dicarbonyl compounds and their use in the construction of the β-methylfuran (**1**), α-methylene γ-lactone (**2**), and β-methylene γ-lactone (**3**) units, common to many furanoid terpenes.[9]


1


2


3

The aldehyde and ketone enol ethers ethoxymethylenecyclohexane (**4**) and 1-methoxycyclohexene (**5**), respectively, served as substrates for 3-diazo-2,4-pentanedione (**6**),[10] methyl 2-diazo-3-oxobutanoate (**7**),[11] and dimethyl diazomalonate