Kinetics of Fast Carbonyl Addition Reactions. II. Carbinolamine Formation between Sarcosine and Pyridine-4-carboxaldehyde

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Abstract: The equilibrium constant for carbinolamine formation between pyridine-4-carboxaldehyde and sarcosine anion has been determined to be $K = 5.0\ (\pm 0.4)\ M^{-1}$ (25°, ionic strength 1.0 M). The kinetics of this rapid addition reaction have been studied by the temperature-jump relaxation technique. The reaction was found to be subject to general base catalysis (by OH^- and by a second sarcosine anion) and to general acid catalysis (by another sarcosine zwitterion molecule). For the uncatalyzed formation reaction a rate constant $k = 1.0\ (\pm 0.25) \times 10^4\ M^{-1}\ sec^{-1}$ was obtained. The catalyzed pathways are discussed in terms of a stepwise reaction mechanism with rate-determining proton transfer.

The reactions of secondary amines with carbonyl compounds lead to addition products known as carbinolamines. Carbinolamines are also intermediates in the corresponding reactions of primary amines which finally give Schiff bases. A brief survey of the literature on carbinolamine intermediates was given in the first paper of this series[1] in which the kinetics of addition of piperazine and of piperazine monocation to pyridine-4-carboxaldehyde have been reported. It was found that the carbinolamine formation rate depends very strongly on the basicity of the attacking nitrogen atom. Furthermore, general base catalysis by OH^- and by a second piperazine molecule of the reaction with piperazine and general acid catalysis by diprotonated piperazine of the reaction with piperazine monocation were observed.[1] Another catalytic term was also observed but could not be assigned unambiguously.

In this paper the results of a kinetic study of carbinolamine formation between sarcosine and pyridine-4-carboxaldehyde are reported. The rapidity of the reaction requires again the application of relaxation techniques. Like piperazine, sarcosine (*N*-methylglycine) is a secondary amine. However, having only one amino group, this substrate avoids some of the complications encountered with piperazine and may also provide information about the effects of a neighboring carboxylate group on the kinetics of carbinolamine formation. The reactions of amino acids with certain analogous carbonyl compounds (pyridoxal phosphate) are of considerable biological importance.

Experimental Section

Materials. Pyridine-4-carboxaldehyde (Fluka) was redistilled under a reduced pressure of nitrogen (bp 80–81° (14 mm)) and stored under nitrogen at 0°. Stock solutions of pyridine-4-carboxaldehyde (0.1 M) were stored at 0° and were stable by uv spectral criteria (λ_{max} 285 nm (ϵ_{max} 1500) for equilibrated aldehyde + hydrate, pH 6–11, $\mu = 1.0\ M$) over a period of weeks. Sarcosine (Merck, for biochemical purposes) and other substances (Merck, pro analysi) were used without further purification.

Measurements of pH, Spectra, and Relaxation Times. Much of the experimental technique was as described previously.[1] All measurements were done at 25.0° and at an ionic strength $\mu = 1.0\ M$, adjusted with sodium perchlorate. Reaction solutions were made up in volumetric flasks by the appropriate combination of standard stock solutions of pyridine-4-carboxaldehyde, sarcosine, sodium hydroxide, and sodium perchlorate. pH values were measured with a Polymetron Type 42-D pH meter and a Metrohm EA 120X combined electrode in which the saturated potassium chloride solution had been replaced by a 4.6 M sodium chloride solution in order to prevent precipitation of potassium perchlorate in the glass sinter diaphragm. The pH meter was calibrated with standard buffers (Merck). The concentrations of sarcosine anion were calculated from the known amounts of sodium hydroxide added to standard sarcosine solution. These concentrations agreed with those calculated from the measured pH and pK_a values determined by half-neutralization of a series of sarcosine solutions of differing concentration.

Spectra were recorded on a Beckman DK 2A spectrophotometer. In the kinetic studies the temperature-jump relaxation technique was applied.[2] The apparatus used was of the double beam type, basic design by L. De Maeyer, improved version by C. Rabl. The changes in absorbance were followed at 280 nm (emission line of Hg/Xe high-pressure lamp), close to the absorption maximum of pyridine-4-carboxaldehyde, and monitored by a Tektronix 549 oscilloscope.

Results

Equilibria. By measuring the pH of a series of solutions of varying concentrations of half-neutralized sarcosine, the following protolytic equilibrium constant was obtained under the conditions used in the kinetic studies (25°, $\mu = 1.0\ M$)[3]

$$K_{AH} = \frac{(H^+)[A^-]}{[AH]} = 9.33 \times 10^{-11}\ M\ (pK_{AH} = 10.03)$$

where A^- = sarcosine anion.

Pyridine-4-carboxaldehyde (P) also can accept a proton.

$$K_{PH} = \frac{[H^+][P]}{[PH^+]} = 1.7 \times 10^{-5}\ M\ (pK_{PH} = 4.77)^4$$

The determination of the hydration constant of pyridine-4-carboxaldehyde

$$K_{H_2O} = [P \cdot H_2O]/[P] = 0.67$$

has been described previously.[1]

(1) H. Diebler and R. N. F. Thorneley, *J. Amer. Chem. Soc.*, **95**, 896 (1973).

(2) M. Eigen and L. De Maeyer in "Technique of Organic Chemistry," Vol. VIII, Part II, Interscience, New York, N. Y., 1963.

(3) In this paper (H^+) denotes the apparent hydrogen ion activity as measured under the conditions given in the Experimental Section.

(4) K. Nakamoto and A. E. Martell, *J. Amer. Chem. Soc.*, **81**, 5857 (1959).

The apparent equilibrium constant for carbinolamine formation

$$K_{app} = \frac{[\text{carbinolamine}]}{([P \cdot H_2O] + [P])[A^-]}$$

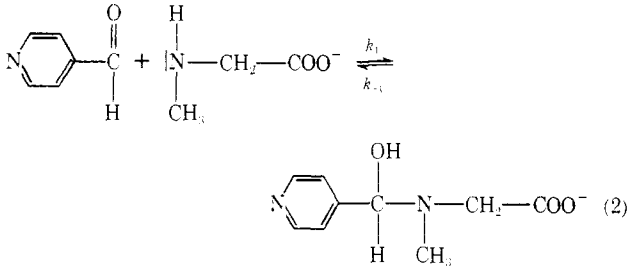
was determined spectrophotometrically. At a given pH, solutions of 4×10^{-4} M total aldehyde, varying amounts of excess sarcosine anion, 0.06–0.27 M, and sodium perchlorate were prepared and the optical density at 290 nm (absorption band of the free aldehyde) was measured as a function of the sarcosine concentration. These measurements were done against reference solutions of the same pH and sarcosine concentration (but without aldehyde) in order to compensate for a small contribution of the sarcosine to the total extinction. The apparent equilibrium constant for carbinolamine formation was evaluated from the slope and intercept of plots of $(E_0 - E)^{-1}$ *vs.* $[A^-]^{-1}$, according to

$$\frac{1}{E_0 - E} = \frac{1}{K_{app}[A^-](E_0 - E_\infty)} + \frac{1}{E_0 - E_\infty} \quad (1)$$

where E = absorbancy at concentration $[A^-]$, E_0 = initial absorbancy ($[A^-] = 0$), and E_∞ = limiting value of the absorbancy at very high $[A^-]$. A value

$$K_{app} = 3.0\ (\pm 0.3)\ M^{-1}$$

which was constant over the pH range pH 9.67–10.48 was obtained. The pH independence of K_{app} indicates that the extent of protonation (of the nitrogen) or deprotonation (of the hydroxyl) of the carbinolamine is negligible under the given conditions. The reaction therefore is



(2)

Multiplying K_{app} by $(1 + K_{H_2O})$ yields the true equilibrium constant

$$K_1 = [C^-]/[P][A^-] = 5.0\ (\pm 0.4)\ M^{-1}$$

where C^- is the carbinolamine product of eq 2. Further evidence in support of eq 2 representing the reaction is the observation of a well-defined isosbestic point at 269 nm (ϵ 1250) and a less well defined one at 239 nm (ϵ 1870). Equilibrium constants calculated from the increase in absorbancy at 258 nm on increasing the sarcosine concentration were in agreement with those calculated from the decrease at 290 nm. The extrapolation of the absorbancy to infinite sarcosine concentration indicated within error no absorption due to the reaction product at 290 nm. This is consistent with the formation of a carbinolamine, which by analogy with the aldehyde hydrate would not be expected to absorb at 290 nm.[4] This also indicates that dehydroxylation to form a Schiff base with a positively charged N atom does not occur to a detectable extent, since such a product would absorb strongly at 290 nm.

Kinetics. The kinetic studies were done under pseudo-first-order conditions with an initial pyridine-4-carboxaldehyde concentration of 4×10^{-4} M and a large excess of sarcosine. As has been discussed before,[1] effects due to the relatively slow relaxation of the aldehyde–hydrate equilibrium can be neglected. The reciprocal relaxation time for the carbinolamine formation–dissociation reaction shown in eq 2 under pseudo-first-order conditions ($[A^-] + [AH] \gg [P]$), at constant pH (buffered by the amine species) and with fast protolytic equilibration $AH + OH^- \rightleftharpoons A^-$, should be given by

$$1/\tau = k_{-1} + k_1[A^-] \quad (3)$$

where k_1 and k_{-1} are the forward and reverse rate constants for the reaction in eq 2.

The experimental data obtained in the pH range 9.40–10.65 are summarized in Table I. Each experimental time constant is the mean of 4–5 individual determinations. The deviations of the individual values from the mean were in most cases within ±4%.

Table I. Experimental Data for the Carbinolamine Formation–Dissociation Reaction between pH 9.40 and 10.65 (25°, μ = 1.0 M; initial concentration of pyridine-4-carboxaldehyde = 4×10^{-4} M)

pH	[Sarcosine anion]	τ, μsec Exptl	τ, μsec Calcd
9.40	0.30	13.6	13.8
	0.24	19.6	19.6
	0.18	30.6	30.0
	0.12	53.4	51.8
	0.06	106	109
	0.03	183	183
9.67	0.27	20.6	20.7
	0.18	37.6	36.8
	0.12	60.5	61.3
	0.06	124	121
	0.036	172	175
	0.012	280	278
10.03	0.30	23.1	22.1
	0.24	29.7	30.3
	0.20	37.0	38.6
	0.16	51.3	50.8
	0.10	83.3	84.7
	0.08	104	104
	0.06	135	131
	0.02	234	235
10.48	0.27	24.6	24.3
	0.18	38.9	38.8
	0.12	57.2	56.6
	0.06	94.4	90.2
	0.036	113	112
	0.024	119	126
10.65	0.30	20.0	19.8
	0.24	25.3	25.7
	0.18	36.0	34.7
	0.12	49.5	49.5
	0.06	73.0	76.0
	0.03	100	98.2

However, at constant pH plots of $1/\tau$ *vs.* $[A^-]$, covering a wide range of concentration from $[A^-] = 0.012$ to 0.30 M, clearly deviated from linearity. This is shown in Figure 1 for some of the data. Actually, the observed relaxation times fit a relationship of the form

$$1/\tau = a + b[A^-] + c[A^-]^2 \quad (4)$$

Values for b and c were obtained from plots of $(1/\tau - a)/[A^-]$ *vs.* $[A^-]$, as shown for two pH values in Figure

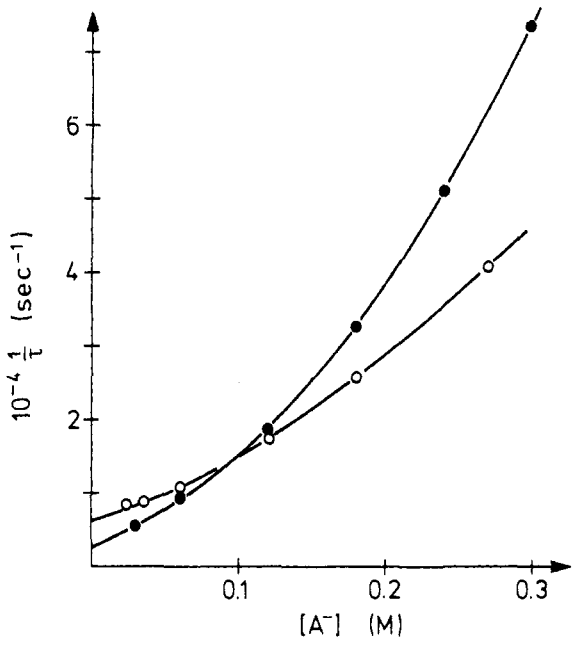


Figure 1. Plots of $1/\tau$ *vs.* the concentration of sarcosine anion at pH 9.40 (●) and 10.48 (○).

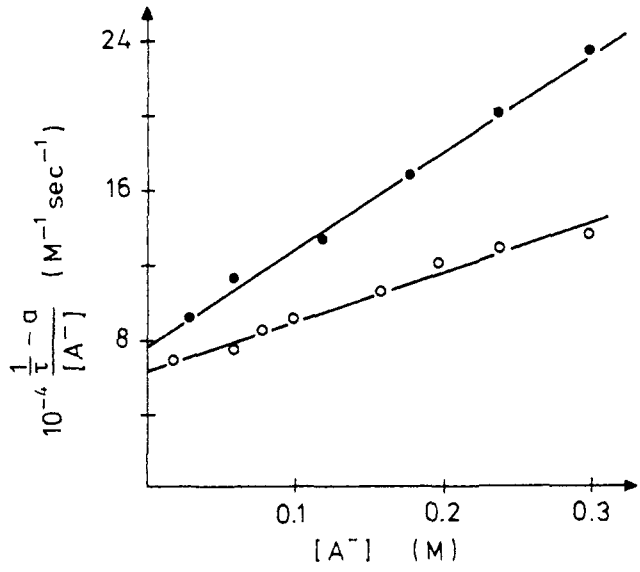


Figure 2. Plots of $(1/\tau - a)/[A^-]$ *vs.* $[A^-]$ at pH 9.40 (●) and 10.03 (○).

Table II. Numerical Values of a, b, and c as Defined by Eq 4 (25°, μ = 1.0 M; estimated errors)

pH	$10^{-3}a$, sec^{-1}	$10^{-4}b$, M^{-1} sec^{-1}	$10^{-5}c$, M^{-1} sec^{-1}
9.40	2.7 (±0.3)	7.6 (±0.7)	5.2 (±0.3)
9.67	2.7 (±0.2)	7.1 (±0.7)	3.6 (±0.3)
10.03	2.9 (±0.4)	6.3 (±0.7)	2.6 (±0.3)
10.48	6.1 (±0.5)	7.0 (±0.7)	2.2 (±0.3)
10.65	7.6 (±0.8)	8.0 (±1)	2.1 (±0.3)

2, with a given by the intercepts of the curves like those in Figure 1 with the $1/\tau$ axis. The values of the coefficients a, b, and c thus obtained are summarized in Table II. The values of τ which are calculated from the figures of Table II *via* eq 4 are given in the last column of Table I for comparison.

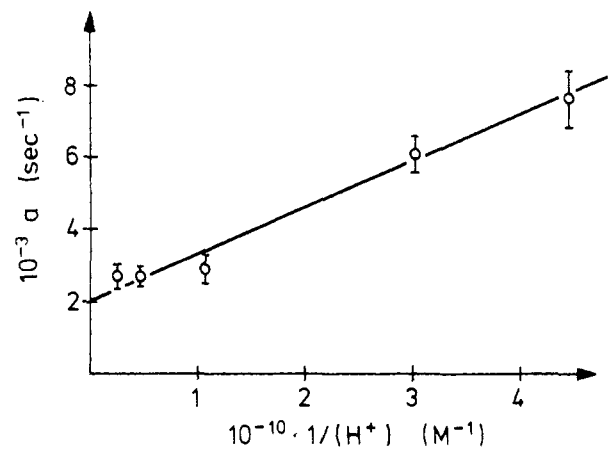


Figure 3. Plot of values of a (eq 4, Table II) *vs.* $1/(H^+)$.

Since carbinolamine formation is a 1:1 reaction of the aldehyde with sarcosine, the second power dependence of the last term in eq 4 on the sarcosine concentration obviously indicates the participation of pathways in which a second sarcosine species acts as a catalyst. The catalytic action may be due to the anion A^- (general base catalysis) or to the zwitterion form AH (general acid catalysis). Base catalysis by OH^- is also likely to occur. Thus one obtains for the overall rate of carbinolamine formation the general expression[5]

$$\frac{d[C^-]}{dt} = k_1[P][A^-] - k_{-1}[C^-] + \sum_i k_1^i[P][A^-][i] - \sum_i k_{-1}^i[C^-][i] \quad (5)$$

where i = A^-, AH, and OH^-. Under the conditions mentioned above (pseudo first order, constant $[H^+]$, fast protolytic equilibration) the following expression for $1/\tau$ (expressed in terms of $[A^-]$) is derived from eq 5

$$1/\tau = k_{-1}^{OH}K_w\frac{1}{(H^+)} + k_{-1} + \left(k_1^{OH}K_w\frac{1}{(H^+)} + k_1 + k_{-1}^{A} + k_{-1}^{AH}\frac{(H^+)}{K_{AH}}\right)[A^-] + \left(k_1^{A} + k_1^{AH}\frac{(H^+)}{K_{AH}}\right)[A^-]^2 \quad (6)$$

with $K_w = \gamma_H[H^+][OH^-] = 1.3 \times 10^{-14}\ M^2$.[1]

Comparison of eq 6 with the empirical relationship eq 4 yields the analytical form of the coefficients a, b, and c. As shown in Figure 3, in which the a values of Table II have been plotted *vs.* $1/(H^+)$, this quantity is of the form

$$a = a_1 + a_2/(H^+)$$

From slope and intercept of Figure 3 and the $[A^-]$-independent terms of eq 6 values for k_{-1} and k_{-1}^{OH} are obtained. With $K_1 = k_1/k_{-1} = 5\ M^{-1}$, the corresponding forward rate constants can also be calculated.

Similarly, the c values of Table II are of the form (Figure 4)

$$c = c_1 + c_2(H^+)$$

(5) Reaction pathways involving the N-protonated pyridine-4-carboxaldehyde can be excluded since this species is completely hydrated according to Nakamoto and Martell.[4]

Table III. Equilibrium and Rate Constants for the Formation of Carbinolamine (C^-) from Pyridine-4-carboxaldehyde (P) and Sarcosine Anion (A^-) (25°, μ = 1.0 M)

Equilibrium	Constant	
$[A^-](H^+)/[AH]$	$K_{AH} = 9.33 \times 10^{-11}$ M	
$[C^-]/[P][A^-]$	$K_1 = 5(\pm 0.4)$ M^{-1}	
Rate term	**Constant**	**Remarks**
$k_{-1}[C^-]$	$k_{-1} = 2.0(\pm 0.5) \times 10^3$ sec^{-1}	
$k_1[P][A^-]$	$k_1 = 1.0(\pm 0.25) \times 10^4$ M^{-1} sec^{-1}	From k_{-1} and K_1
$K_{-1}^{OH}[C^-][OH^-]$	$k_{-1}^{OH} = 1.0(\pm 0.2) \times 10^7$ M^{-1} sec^{-1}	
$k_1^{OH}[P][A^-][OH^-]$	$k_1^{OH} = 5.0(\pm 1) \times 10^7$ M^{-2} sec^{-1}	From k_{-1}^{OH} and K_1
$k_1^{A}[P][A^-][A^-]$	$k_1^{A} = 1.9(\pm 0.3) \times 10^5$ M^{-2} sec^{-1}	
$k_{-1}^{A}[C^-][A^-]$	$k_{-1}^{A} = 3.8(\pm 0.6) \times 10^4$ M^{-1} sec^{-1}	From k_1^{A} and K_1
$k_1^{AH}[P][A^-][AH]$	$k_1^{AH} = 7.5(\pm 1) \times 10^4$ M^{-2} sec^{-1}	
$k_{-1}^{AH}[C^-][AH]$	$k_{-1}^{AH} = 1.5(\pm 0.2) \times 10^4$ M^{-1} sec^{-1}	From k_1^{AH} and K_1

Comparison with the coefficient of $[A^-]^2$ in eq 6 yields values for k_1^{A} and k_1^{AH}, and (with K_1) also for the reverse rate constants. A summary of the results obtained is given in Table III.

With these data, the values of the coefficient of $[A^-]$ in eq 6, which should be identical with b of eq 4, can now be calculated. One obtains coeff $\times 10^{-4}$ = 8.1 M^{-1} sec^{-1} (pH 10.65), 7.3 M^{-1} sec^{-1} (10.48), 7.0 M^{-1} sec^{-1} (10.03), 8.5 M^{-1} sec^{-1} (9.67), and 11.3 M^{-1} sec^{-1} (9.40). In view of the general errors involved, these values compare quite well with those of b given in Table II and thus confirm that the assumed mechanism is consistent with the results. The agreement between the two sets of b values is somewhat less satisfactory at the lowest pH values. This may be due to a medium effect. At low pH and high sarcosine anion concentrations large amounts of sarcosine zwitterion are necessarily present (highest concentration: [AH] = 1.28 M at pH 9.40, $[A^-]$ = 0.30 M), which have not been considered in adjusting the ionic strength. To test for such a medium effect, the relaxation time of a solution of 0.12 M sarcosine anion + 4 $\times 10^{-4}$ M pyridine-4-carboxaldehyde, pH 10.65, μ = 1.0 M, 25°, was measured, τ = 50 μsec, and then remeasured after addition of 1.0 M N-trimethylglycine (Betain), giving τ = 65 μsec. Thus high concentrations of the nonreactive zwitterion Betain do indeed produce an appreciable medium effect. This effect was not investigated further, however, since Betain which has three hydrophobic methyl groups may produce medium effects quite different from those of sarcosine zwitterion.

Discussion

The pK for addition of a proton to sarcosine anion is 10.03, a value very close to that for piperazine (9.97). However, the stability constant for carbinolamine formation of sarcosine anion with pyridine-4-carboxaldehyde, K_1 = 5 (± 0.4) M^{-1}, is a factor of 10 smaller than in the case of piperazine[1] and practically identical with that of alanine, K = 4.8 M^{-1}.[6a] It has been discussed in detail[6] that the equilibrium constants for carbinolamine formation show little sensitivity to the basicities of the amines and that the differences in the equilibrium constants which are actually observed are difficult to account for. A comparison of the kinetic data for carbinolamine formation with piperazine[1] and with sarcosine anion shows that the higher stability of

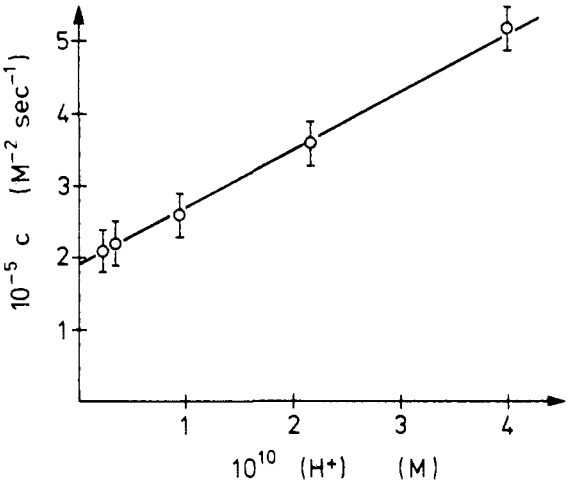
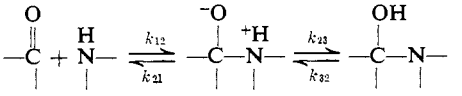


Figure 4. Plot of values of c (eq 4, Table II) *vs.* (H^+).

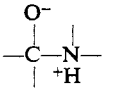
piperazine–carbinolamine is largely due to a faster formation rate.

In analogy to similar addition reactions[7-9] a two-step mechanism is assumed for the carbinolamine formation reaction under study (eq 7) with proton transfer



(7)

as the rate-determining step,[1,10,11] *i.e.* $k_{21} \gg k_{23}$. Since the dipolar intermediate is a rather unstable species,[8,9] the steady-state approximation may be applied. The apparent formation rate constant for the uncatalyzed reaction is then given by $k_1 = k_{23}k_{12}/k_{21}$ and the reverse rate constant by $k_{-1} = k_{32}$. Molecular models suggest that the most likely configuration of the zwitterion is one in which the proton is relatively far away from the oxygen



(6) (a) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968); (b) J. Hine and R. D. Weimar, *J. Amer. Chem. Soc.*, 87, 3387 (1965).

(7) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 490 ff.

(8) J. E. Reimann and W. P. Jencks, *J. Amer. Chem. Soc.*, 88, 3973 (1966).

(9) (a) J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970); (b) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

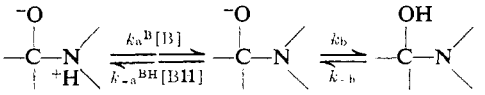
(10) R. E. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2358 (1969).

(11) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 3262 (1972).

and that direct (N to O) proton transfer and H_2O mediated concerted proton transfer are affected by steric hindrance.

As shown in this study, the addition of sarcosine anion to pyridine-4-carboxaldehyde is subject to general base catalysis by OH^- and by a second sarcosine anion, and it is also subject to general acid catalysis by the neutral (*i.e.*, zwitterion) sarcosine molecule. The observed general acid–base catalysis can be rationalized in terms of proton transfer with the catalyzing species. The estimates which have to be made for the corresponding rate constants are based on the general rules for proton transfer[12] and a considerable amount of experimental material.[12,13] All the proton transfer steps under consideration are slightly affected by steric shielding, whereas the effect of the electrostatic interaction between reactants of the charge type -1, -1 on the rate of reaction is almost negligible at ionic strength 1.0 *M*.

For catalysis by a general base B the mechanism in eq 8 is assumed.[11,14] Proton donors for the second



(8)

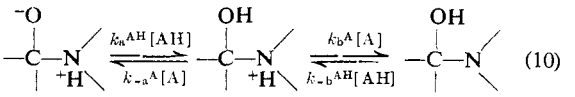
(forward) step are H_2O and AH. The steady-state expression for the apparent forward rate constant of such a catalyzed pathway is given by

$$k_1^{B} = \frac{k_{12}}{k_{21}} k_a^{B} \frac{k_b^{H_2O} + k_b^{AH}[AH]}{k_{-a}^{BH}[BH] + k_b^{H_2O} + k_b^{AH}[AH]} \quad (9)$$

From the pK values for protonation of N and of O of the intermediate of eq 8 (see later) it can be concluded that $k_{-a}^{H_2O} \ll k_b^{H_2O}$. (Furthermore, under almost all experimental conditions is $k_b^{AH}[AH] \ll k_b^{H_2O}$, since $k_b^{H_2O} \approx 3 \times 10^9$ sec^{-1}). Thus for B = OH^-, eq 9 simplifies to $k_1^{OH} = k_a^{OH} k_{12}/k_{21}$; *i.e.*, the first proton transfer step is rate determining. The reaction of the zwitterion with OH^- is certainly diffusion controlled; its rate constant k_a^{OH} is estimated to be close to 4×10^9 M^{-1} sec^{-1}. With $k_1^{OH} = 5 \times 10^7$ M^{-2} sec^{-1}, it follows that $k_{12}/k_{21} \approx 1.3 \times 10^{-2}$ M^{-1}. This value for the equilibrium between the reactants (aldehyde and amine) and the zwitterion carbinolamine is smaller by a factor $\sim$16 than in the case of piperazine. For the equilibrium between the zwitterion and the neutral (except for the charge of the sarcosine's carboxylic group) carbinolamine results $k_{23}/k_{32} = K_1 k_{21}/k_{12} \approx 400$ (piperazine: 250).

Similarly, for sarcosine anion as catalyzing base is obtained $k_1^{A} \approx k_a^{A} k_{12}/k_{21}$. Since $k_1^{A} = 1.9 \times 10^5$ M^{-2} sec^{-1}, therefore, $k_a^{A} \approx 1.5 \times 10^7$ M^{-1} sec^{-1}. Clearly, this value is well below the diffusion controlled limit. With some uncertainty, the rate constant k_{-a}^{AH} for the reverse process may be estimated to be about 5×10^8 M^{-1} sec^{-1}. Since the pK_a of AH is 10.0, these data give for the pK_a of the zwitterion carbinolamine a value close to 11.5, and (with $k_{23}/k_{32} \approx 400$) for the p$K_a$ of the neutral carbinolamine a value close to 14.1. Similar values have been obtained for the piperazine system.[1] In order to provide a complete characterization of the sarcosine carbinolamine, knowledge about two more pK values is required, those for addition of a proton to the zwitterion and to the neutral carbinolamine. A crude estimate of their values may be obtained in the following way. According to a recent paper,[16] protonation of the nitrogen of the carbinolamine formed from acetaldehyde and methylamine decreases the pK_a of the OH group by 4.7 units, and ionization of the OH group increases the pK of the nitrogen by 4.7 units. These shifts are probably of similar magnitude for carbinolamines of pyridine-4-carboxaldehyde; *i.e.* the pK for addition of a proton to the zwitterion carbinolamine under consideration may be expected to be around 9.4 and for addition to the neutral carbinolamine around 6.8.

The acid-catalyzed pathway can be rationalized by the mechanism



(10)

Under the given conditions it is mainly the sarcosine anion which acts as acceptor in the second proton transfer step. According to the estimated pK values it is to be expected that k_b^{A} is only slightly larger than k_{-a}^{A}.[12] Therefore, from $k_1^{AH} = (k_{12}/k_{21}) k_a^{AH} k_b^{A}/(k_{-a}^{A} + k_b^{A}) = 7.5 \times 10^4$ M^{-2} sec^{-1} (Table III) it follows that $k_a^{AH} \approx 1 \times 10^7$ M^{-1} sec^{-1}. This value is of a reasonable magnitude for a thermodynamically slightly unfavorable proton transfer step ($\Delta pK \approx -0.6$, according to the estimated pK value for protonation of the zwitterion) which in addition is affected by some steric shielding.

A mechanism analogous to eq 10 but with H_2O as the proton donor of the first step probably contributes appreciably to the "uncatalyzed" proton transfer. Assuming a value of 5×10^9 M^{-1} sec^{-1} for the diffusion controlled rate constant k_{-a}^{OH} leads to $k_a^{H_2O} \approx 2 \times 10^5$ sec^{-1}. This value is not far from that of k_{23} which from $k_1 = k_{23} k_{12}/k_{21} = 1 \times 10^4$ M^{-1} sec^{-1} is obtained to be $k_{23} \approx 8 \times 10^5$ sec^{-1} (in the piperazine system: $k_{23} \approx 1 \times 10^6$ sec^{-1} [1]).

The results of this study, when compared to those for the piperazine system, give no evidence for characteristic changes in the mechanism of carbinolamine formation due to the sarcosine's carboxylic group. Actually, the mechanisms appear to be completely analogous. The formation rate constants, however, show significant differences. Those for sarcosine are consistently lower, by factors of $\sim$20–40. This applies to the uncatalyzed reaction (k_1) as well as to the catalyzed pathways (k_1^{OH}, k_1^{A}) and is mainly due to a lower preequilibrium constant, k_{12}/k_{21}. Steric factors and inductive effects of the carboxylic group may contribute to the lower stability of the dipolar addition product with sarcosine anion.

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(12) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(13) M.-L. Ahrens and G. Maass, *Angew. Chem.*, **80**, 848 (1968).
(14) See also the detailed discussion of general base catalysis of simple carbonyl addition reactions given recently by Sayer and Jencks;[15] the dipolar addition product of a strongly basic amine may have a sufficient lifetime to enable a stepwise reaction mechanism of this type.
(15) J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, **95**, 5637 (1973).
(16) M. I. Page and W. P. Jencks, *J. Amer. Chem. Soc.*, **94**, 8828 (1972); see footnote 30.