A Proton Nuclear Magnetic Resonance Study of the Aqueous Chemistry of Acetaldehyde and Ammonia. The Formation of 2,4,6-Trimethylhexahydro-s-triazine[1]

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Received April 12, 1973

Proton magnetic resonance techniques were used to study the reaction of ammonia with acetaldehyde. At high pH and 10° significant amounts of ammonia adducts were detected by observing their methyl resonances, which occurred in the region of the acetaldehyde hydrate methyl group (δ 1.65). The adduct which predominates at ammonia/aldehyde ratios of >1 has been identified as the cyclic trimer 2,4,6-trimethylhexahydro-s-triazine, $(CH_3CHNH)_3$. By varying concentrations and pH we have determined the equilibrium constant $K_T = [(CH_3CHNH)_3]/[CH_3CHO]^3[NH_3]^3 = 2.0 \pm 0.6 \times 10^9\ M^{-5}$ at 10°. The pK_a for dissociation of the protonated trimer was 8.36 ± 0.05 at 10°. Two other species were observed and have been tentatively identified as the dimeric compounds $CH_3CH(OH)NHCH(OH)CH_3$ and $CH_3CH(NH_2)NHCH(OH)CH_3$. The trimer was found to be stable in aqueous solution at pH ≥10, but was reversibly dissociated to acetaldehyde and free ammonia by lowering the pH to 7. The methyl resonance of acetaldehyde exhibited a characteristic line broadening which increased linearly with ammonia concentration but decreased with increasing temperature. These effects were analyzed in terms of a three-site chemical exchange problem

$$CH_3CHO + NH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3CH(OH)NH_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} CH_3CH{=}NH + H_2O$$

From this analysis the following limits were placed on the rate constants for the addition of ammonia to acetaldehyde at pH 7, 10°: $k_{-1} > 300\ \text{sec}^{-1}$, $k_1 \gtrsim 10^4\ M^{-1}\,\text{sec}^{-1}$, $2 \leq K_1 \leq 17\ M^{-1}$.

In connection with investigations on ethanolamine ammonia lyase, an enzyme that has been postulated to catalyze the conversion of ethanolamine to acetaldehyde and ammonia *via* the intermediate 1-aminoethanol,[3] it became desirable to study the reaction between acetaldehyde and ammonia in aqueous solution. Though there has been little study of this particular reaction, it is a member of an extensively studied class of reactions involving the nucleophilic addition of amines and related compounds to a carbonyl group (eq 1).[4]

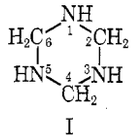
$$R_1R_2C{=}O + RNH_2 \rightleftharpoons R_1R_2C(OH)NHR \qquad (1)$$

The product of eq 1, a tetrahedral adduct termed a carbinolamine, cannot in general be isolated as a stable intermediate,[5] since it readily undergoes dehydration to an imine or similar compound (eq 2).

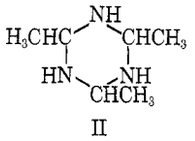
$$R_1R_2C(OH)NHR \rightleftharpoons R_1R_2C{=}NR + H_2O \qquad (2)$$

In a study of semicarbazone and oxime formation, Jencks demonstrated that an intermediate carbinolamine was involved in the two-step mechanism by which these compounds are produced.[6] Later, Cordes and Jencks showed conclusively that the hydrolysis of a Schiff base to a carbonyl compound and an amine involved the formation of the carbinolamine.[7] At neutral or alkaline pH hydration of the imine (eq 2) was rate determining in the hydrolysis, while at lower pH elimination of the amine from the tetrahedral adduct (eq 1) was rate determining. In an extensive series of investigations Hine and coworkers have studied the kinetics and catalysis of the reaction of isobutyraldehyde with various aliphatic primary amines to form imines.[8] Their results concerning mechanism agree with those of Cordes and Jencks.

The reactions between the simpler aldehydes and amines are more difficult to study because of the formation of oligomers. For instance, formaldehyde reacts with ammonia to produce hexamethylenetetramine by way of the trimer, hexahydro-s-triazine (I).[9] With primary amines, such as methylamine and aniline, formaldehyde reacts to form 1,3,5-substituted hexahydro-s-triazines.[4a,10] A similar cyclic trimer, 2,4,6-trimethylhexahydro-s-triazine (II), has been shown to



I



II

be formed by the reaction of ammonia with acetaldehyde in ether solution.[11] A common feature of these polymerizations is that oligomer formation is believed

(1) This research was supported in part by Public Health Service Grants AM-09115, AM-16589, and RR-05598 (B. M. B.) and GM-17190 (B. D. S.), and a grant to B. M. B. from The Medical Foundation, Inc.

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(3) B. M. Babior, *J. Biol. Chem.*, **245**, 6125 (1970).

(4) This general type of reaction has been the subject of several comprehensive reviews: (a) M. M. Sprung, *Chem. Rev.*, **26**, 297 (1940); (b) E. C. Wagner, *J. Org. Chem.*, **19**, 1862 (1954); (c) W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964); (d) V. A. Palm, U. L. Haldna, and A. J. Talvik, "The Chemistry of the Carbonyl Group," Vol. 1, S. Patai, Ed., Interscience, New York, N. Y., 1966, p 421; (e) R. L. Reeves, *ibid.*, p 567; (f) Y. Ogata and A. Kawasaki, "The Chemistry of the Carbonyl Group," Vol. 2, J. Zabicky, Ed., Interscience, New York, N. Y., 1970, p 1.

(5) Poziomek, *et al.*, were able to isolate the hydroxylamine, hydrazine, and phenylhydrazine adducts of 2-formyl-1-methylpyridinium iodide. The *n*-butylamine adduct was not stable enough for complete characterization: E. J. Poziomek, D. N. Kramer, B. W. Fromm, and W. A. Mosher, *J. Org. Chem.*, **26**, 423 (1961).

(6) W. P. Jencks, *J. Amer. Chem. Soc.*, **81**, 475 (1959).

(7) (a) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962); (b) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963).

(8) J. Hine and F. A. Via, *ibid.*, **94**, 190 (1972).

(9) H. H. Richmond, G. S. Myers, and G. F. Wright, *J. Amer. Chem. Soc.*, **70**, 3659 (1948).

(10) E. M. Smolin and L. Rapoport, "The Chemistry of Heterocyclic Compounds. s-Triazine and Derivatives," Interscience, New York, N. Y., 1959.

(11) O. Aschan, *Chem. Ber.*, **48**, 874 (1915).

TABLE I

NMR PARAMETERS FOR THE METHYL GROUPS IN ACETALDEHYDE (A) AND HYDRATE (AOH)[a]

Temp, °C	$\delta_A^{H_2O}$	$\delta_A^{CH_3CN}$	^3J_A	$\Delta\nu^*_A$	δ^A_{AOH}	$^3J_{AOH}$	$\Delta\nu^*_{AOH}$
10	−2.648	0.170	3.04 ± 0.03	0.04	−0.919	5.27 ± 0.02	0.20
25	−2.507	0.168	2.97 ± 0.02	0.04	−0.918	5.22 ± 0.02	0.21
34	−2.414	0.164	2.97 ± 0.01	0.06	−0.914	5.21 ± 0.03	0.23

[a] The chemical shift of species X relative to Y is given in parts per million as δ^Y_X, where downfield shifts are taken as positive; line widths and coupling constants are in Hz. The samples contained 0.40 *M* CH_3CHO, 0.63 *M* CH_3CN, 0.50 *M* NH_4Cl + KCl, and 0.10 *M* phosphate buffer at pH 7.0.

to involve the imine formed from the initial carbinolamine.

Nmr spectroscopy appeared to us to be an appropriate technique for the investigation of the aqueous chemistry of simple aldehydes and amines, since nonchromophoric species could be observed and kinetic information could be obtained from systems at equilibrium. In the present communication we report the results of an investigation of the reaction between acetaldehyde and ammonia as studied by this technique.

Results

All of the proton nmr results presented in this section were obtained at 100 MHz. Details of the techniques used are summarized in the Experimental Section. The general features of nmr spectra of acetaldehyde in aqueous solution are well known; if the H_2O resonance occurs at δ 5.0, then the methyl doublet and methine quartet for acetaldehyde appear at δ 2.55 and 10.0, respectively, while the corresponding resonances for the hydrate of acetaldehyde appear at δ 1.65 and 5.55. Since the H_2O resonance makes the observation of weak resonances in the δ 4–6 region quite difficult, we have examined in detail only the methyl region δ 1–3.

Hydration of Acetaldehyde.—In many of the following experiments, it was necessary to determine the individual concentrations of acetaldehyde and its hydrate in aqueous solution when only one species could be measured. This determination was made from the concentration of the observed species and the equilibrium constant for the reaction acetaldehyde + $H_2O \rightleftharpoons$ hydrate. Preliminary studies were therefore performed on the effect of pH, temperature, and ionic strength on this equilibrium.

The nmr parameters for the methyl group doublets in acetaldehyde and its hydrate are presented in Table I, with chemical shifts and line widths reported for samples containing no ammonia. The line width $\Delta\nu^*$ used throughout this paper is the residual line width (the observed line width minus the line width of the reference peak). This parameter can be used for comparison of line widths obtained under nonidentical conditions of magnetic field homogeneity. The substantial difference in line widths for the aldehyde and hydrate is believed to be the result of a large difference in proton relaxation times. Spin-lattice relaxation times T_1 were measured for the two methyl groups in D_2O at 35° (solutions not degassed) using the conventional Fourier transform inversion–recovery method.[12] The results for acetaldehyde and its hydrate were 11.4 ± 0.4 and 3.25 ± 0.15 sec, respectively.

(12) R. L. Vold, J. S. Waugh, M. P. Klein, and D. E. Phelps, *J. Chem. Phys.*, **48**, 3831 (1968).

Peak area measurements allow the computation of the hydration equilibrium constant.

$$K_h = [CH_3CH(OH)_2]/[CH_3CHO] \quad (3)$$

Table II presents hydration constants obtained in these studies. For comparison, the values of Bell and

TABLE II

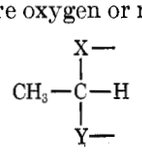
HYDRATION EQUILIBRIUM CONSTANTS

Temp, °C	pH	μ	K_h[a]	K_h[b]
10	4.8–10.5	0.5–1.7	1.92	1.74 ± 0.05
	7.4	0.3		2.11[c]
25	7.0	0.6	1.58	1.19 ± 0.05
34	7.0	0.3	0.93	0.90 ± 0.05
	7.0	0.6		0.84 ± 0.02
	7.4	0.1		1.07[c]
	7.4	0.3		0.91[c]

[a] R. P. Bell and J. C. Clunie, *Trans. Faraday Soc.*, **48**, 439 (1952). [b] Results of this work. [c] Results obtained in D_2O; pD is given.

Clunie obtained by optical methods are included. These authors used 0.02 *M* acetaldehyde and zero ionic strength, while our data are for 0.3–0.4 *M* aldehyde and rather high ionic strengths. Our results are in general agreement with those of previous workers,[13] indicating that K_h is independent of pH over the range of interest but decreases with increasing temperature or ionic strength.

Identity and Properties of the Major Adduct Formed from Acetaldehyde and Ammonia.—Nmr spectra of solutions containing approximately 0.2–0.5 *M* acetaldehyde and NH_4Cl at pH >7 show methyl resonances from species other than acetaldehyde and its hydrate (see Figure 1). The appearance of these additional resonances depended upon both acetaldehyde and NH_3 concentration, indicating that they could not be accounted for by impurities in the reagents. The chemical shifts of these new methyl groups were sensitive to pH but always appeared in the same region as the hydrate methyl (designated H) indicating the structure III, where X and Y are oxygen or nitrogen.



III

Although several compounds were present, at a sufficiently high pH and NH_3 concentration one species (^3J = 6.25 Hz) predominated (designated T in Figure 1).

Similar nmr spectra were obtained for aqueous solutions of commercial "acetaldehyde–ammonia" (com-

(13) L. C. Gruen and and P. T. McTigue, *J. Chem. Soc.*, 5217 (1963).

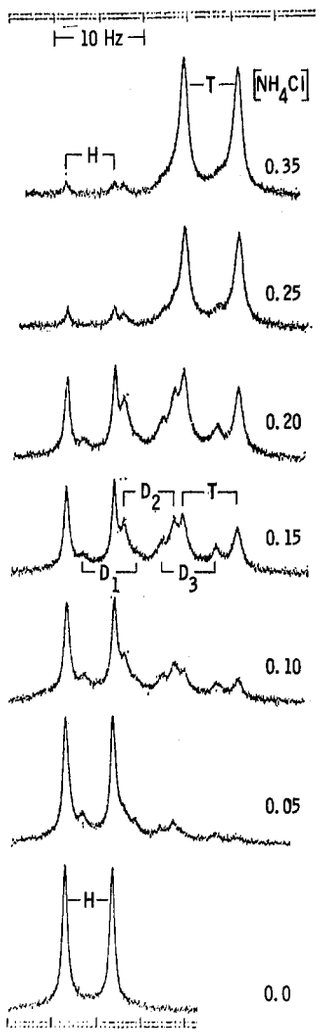


Figure 1.—Nmr spectra of the adduct methyl region for samples containing 0.42 *M* CH_3CHO, 0.067 *M* CH_3CN, 0.50 *M* NH_4Cl + KCl, 0.10 *M* phosphate at pH 10.5 at 10°.

pare the high pH spectrum in Figure 2 with the high ammonia concentration spectrum in Figure 1). [Infrared[14,15] and mass spectroscopy confirmed that the commercial reagent was 2,4,6-trimethylhexahydro-*s*-triazine (II), as had been previously indicated by X-ray studies.[16]]

These nmr spectra, taken in several deuterated solvents at 10 and 35°, showed a single doublet (^3J = 6.05–6.21 Hz) for the trimer methyl groups and a single quartet for the methine protons 2.51–2.61 ppm downfield from the doublet. The ratio of the doublet area to the quartet area was 3.03. A broad peak whose chemical shift varied with solvent and temperature represents the exchangeable protons of –NH– in equilibrium with those of water of hydration. The ratio of this peak area to the methine quartet was 3.0 ± 0.2 in pyridine and acetone at 10 and 35°, consistent with the formula $(CH_3CHNH)_3 \cdot 3H_2O$. A small amount of acetaldehyde was often observed, indicating that some dissociation had occured. The most important feature

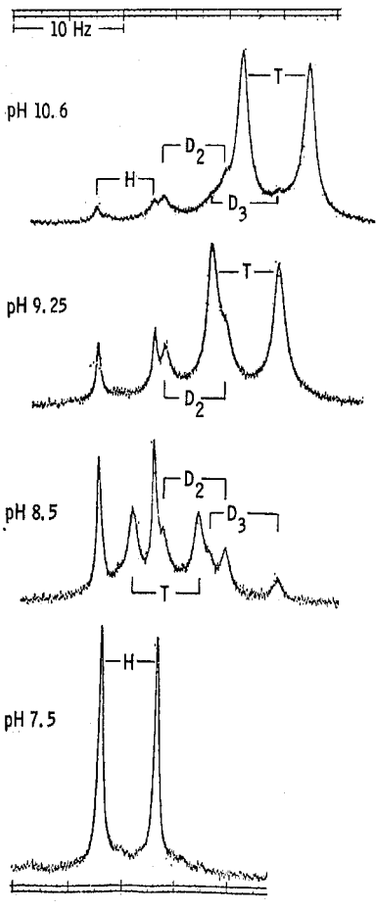


Figure 2.—Nmr spectra of the adduct methyl region for commercial "acetaldehyde–ammonia" (0.16 *M*) in 0.10 *M* phosphate buffer at 10°.

of these results is that the spectrum of the "acetaldehyde–ammonia" trimer in D_2O shows no significant differences (other than the position of the OH resonance) from those in other solvents, indicating that the trimer can exist in aqueous solution.

The difference in chemical shift of 2.55 ppm between the methyl and methine protons may be compared with corresponding values for acetaldehyde hydrate and paraldehyde of 3.9 and 3.7 ppm, respectively. This characteristic upfield shift of the methine proton for the trimer is consistent with the replacement of oxygens by nitrogens on the methine carbon. The methyl–methine coupling constant of 6.2–6.3 Hz observed in D_2O and H_2O solutions agrees with that obtained by Booth, *et al.*,[17] for the 2,6-methyl doublets of 2,6-dimethyl- and 2,4,6-trimethylpiperidine.

Spectra of completely dry, sublimed "acetaldehyde–ammonia" in acetone-d_6 show no detectable peak for OH, NH or at best a very broad, weak resonance centered near the methyl doublet. The NH proton is expected to have a large line width (short T_2) owing to strong scalar relaxation from quadrupolar relaxed ^{14}N. If intermolecular exchange is slow or hydrogen-bonded dimers are not favored owing to steric interference, then it is not unreasonable to find the NH resonance too broad to detect. This effect has been observed for diisopropylamine.[18]

(14) C. J. Pouchert, "Aldrich Library of Infrared Spectra," 1970, p 154B.
(15) C. W. Hoerr, E. Rapkin, A. E. Brake, K. N. Warner, and H. J. Harwood, *J. Amer. Chem. Soc.*, **78**, 4667 (1956); H. H. Fox, *J. Org. Chem.*, **23**, 468 (1958).
(16) E. W. Lund, *Acta Chem. Scand.*, **5**, 678 (1951); E. W. Lund, *ibid.*, **12**, 1768 (1958).
(17) H. Booth, J. H. Little, and J. Feeney, *Tetrahedron*, **24**, 279 (1968).
(18) R. A. Murphy and J. C. Davis, Jr., *J. Phys. Chem.*, **72**, 3111 (1968).

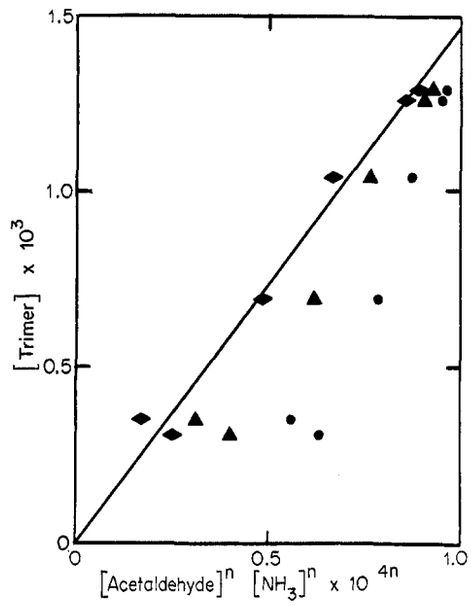


Figure 3.—Plot of the 2,4,6-trimethylhexahydro-*s*-triazine molar concentration *vs.* the concentration term $[\text{acetaldehyde}]^n[\text{NH}_3]^n \times 10^{4n}$ where $n = 1$ (●), $n = 2$ (▲), and $n = 3$ (◆). A least-squares fitted line for the equation $[\text{T}] = K_\text{T}[\text{A}]^3[\text{NH}_3]^3$ is shown with slope $K_\text{T} = 1.47 \times 10^9\ M^{-5}$. Data are from sample set d_2 in Table IV, pH 7.00 at 10°.

Further evidence that the commercial material was in equilibrium with acetaldehyde and ammonia was provided by experiments showing that acidification of aqueous solutions of "acetaldehyde–ammonia" (normally pH ~11) resulted in dissociation of the trimer (Figure 2). At 10° and pH 10.6 about 65% of the methyl resonances can be accounted for as trimer and 5% as aldehyde and hydrate, while at pH 7.5 there is about 80% aldehyde and hydrate.

Comparison of the nmr spectrum of an ammoniacal solution of acetaldehyde (Figure 1) with that of commercial "acetaldehyde–ammonia" (Figure 2) shows that in both cases the major ammonia adduct existing in solution is 2,4,6-trimethylhexahydro-*s*-triazine. The results shown in Figure 2 could also be produced using mixtures of acetaldehyde and ammonia and varying the pH from 7 to 10. Thus, the nmr results demonstrate that in aqueous solution the triazine trimer is in equilibrium with free acetaldehyde and ammonia along with other intermediate species, and that this equilibrium can be shifted from one extreme to the other by varying pH.

The chemical shift of the triazine methyl doublet exhibited a sigmoidal dependence on pH characteristic of species involved in a rapid protonation equilibrium.[19] The observed chemical shift can be expressed as

$$\delta_\text{obsd} = \delta_\text{T}^+ + \left(\frac{K_\text{A}}{K_\text{A} + [\text{H}^+]}\right)(\delta_\text{T} - \delta_\text{T}^+) \qquad (4)$$

where δ_T^+ and δ_T are the chemical shifts of the protonated and unprotonated forms and K_A is the acid dissociation constant for the protonated amine. Using a generalized nonlinear least-squares treatment[20] it was possible to calculate from the δ_obsd *vs.* $[\text{H}^+]$ data that at 10° and ~1.6 *M* ionic strength

$$\delta_{\text{T}^+}^{\text{CH}_3\text{CN}} = -0.666 \pm 0.003 \text{ ppm}$$
$$\delta_\text{T}^{\text{CH}_3\text{CN}} = -0.899 \pm 0.006 \text{ ppm}$$
$$\text{p}K_\text{A} = 8.36 \pm 0.05$$

The difference in the chemical shift of the methyl doublet between the protonated and unprotonated forms is 0.23 ppm, in good agreement with an expected difference of about 0.30 ppm for compounds with the structure CH_3CN.[21] In comparing our pK_A with known values, we find that piperidine, piperazine, and hexamethylenetetramine, which are cyclic amines with one, two, and four nitrogens, have pK_A's at 25° of 11.2, 9.8, and 6.2, respectively.[22] Thus, our pK_A is consistent with the triazine structure.

Further evidence that the trimer is the major ammonia adduct in aqueous solution was the cubic dependence of the concentration of the adduct on the concentrations of acetaldehyde and ammonia. This dependence was established by experiments showing that a plot (Figure 3) of the trimer concentration (T) against the concentration term $[\text{CH}_3\text{CHO}]^n[\text{NH}_3]^n$ gave a straight line passing through the origin only for $n = 3$, consistent with the reaction

$$3\text{CH}_3\text{CHO} + 3\text{NH}_3 \overset{K_T}{\rightleftharpoons} \text{trimer} \qquad (5)$$

The concentrations of the various unprotonated species in solution were calculated from peak area measurements using a pK_A for ammonia corrected for the temperature and ionic strength (see Experimental Section) and the measured pK_A for the trimer. From the slopes obtained in several experiments, where ammonia concentration, aldehyde concentration, or pH were varied, we have determined a value for K_T, the equilibrium constant for trimer formation, of $2.0 \pm 0.6 \times 10^9\ M^{-5}$ at 10°. This equilibrium constant (as well as all others presented in this report) is expressed in terms of free acetaldehyde concentration, rather than aldehyde plus hydrate.

Other Ammonia Adducts.—Adducts other than the trimer appear consistently in solutions of the trimer and in acetaldehyde and ammonia mixtures. An nmr study of the ammonia concentration dependence of these adducts was conducted at pH 10.5 and 10°. Spectra obtained for the adduct methyl region are shown in Figure 1. Three doublets can be distinguished in addition to those corresponding to hydrate (H) and trimer (T) (see Table III). The relative sizes of the various peaks were found to be a function of NH_3 concentration. At low ammonia con-

TABLE III
ADDUCT METHYL DOUBLETS AT pH 10.5, 10°

Doublet	$\delta^{\text{CH}_3\text{CN}}$, ppm	^3J, Hz
Hydrate	−0.746	5.25
D_1	−0.767	5.7–5.8
D_2	−0.811	5.6–5.7
D_3	−0.858	6.1–6.2
Trimer	−0.882	6.2

(19) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, Chapter 10.

(20) N. Arley and K. R. Buch, "Introduction to the Theory of Probability and Statistics," Wiley, New York, N. Y., 1950; I. S. Sokolnikoff and E. S. Sokolnikoff, "Higher Mathematics for Engineering and Physics," McGraw-Hill, New York, N. Y., 1941.

(21) G. Slomp and J. G. Lindberg, *Anal. Chem.*, **39**, 60 (1967).

(22) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 2.

centrations the adduct peaks D_1, D_2, and D_3 were larger than those of the trimer. As ammonia concentration increased, the trimer peaks increased while D_1 decreased; D_2 and D_3 together reached a maximum at 0.20 *M* NH_4Cl but decreased as NH_4Cl was increased to 0.35 *M*. The doublets D_2 and D_3 were also clearly observed in experiments concerned with the pH dependence of solutions of the trimer (Figure 2) and acetaldehyde and ammonia mixtures. These two doublets showed a parallel change in chemical shift toward lower field as pH was decreased below 8, suggesting an amine with $pK_A = 7$–8. These findings suggest that peaks D_2 and D_3 correspond to a single adduct while peak D_1 belongs to a separate species. The possible nature of these additional adducts will be considered in the Discussion.

Line Broadening of Acetaldehyde in the Presence of Ammonia.—Kinetic information on the reaction of acetaldehyde with ammonia was obtained by a study of the line width of the acetaldehyde methyl group as a function of ammonia concentration *at pH 7*. Because of technical problems arising from the exchange of acetaldehyde methyl protons with D_2O solvent when ammonia was present, all of these experiments were carried out in H_2O solution. A series of samples were prepared with an initial acetaldehyde concentration of 0.32–0.40 *M;* the NH_4Cl concentration was varied from zero to 1.6 *M*, maintaining constant ionic strength with KCl. Under these conditions at pH 7 significant line broadening was observed for acetaldehyde while only small amounts of adducts were formed.

There appeared to be no dependence of line width on phosphate or acetaldehyde concentration. However, the line width of the aldehyde methyl doublet increased linearly with increasing NH_4Cl concentration; the line width of the hydrate was unaffected. At NH_4Cl concentrations above 0.40 *M* at 10° we observed the appearance of ammonia adducts described in previous sections. When necessary, the concentration of free NH_4^+ was corrected for these adducts (mostly trimer) by a procedure described in the Experimental Section.

The dependence of line broadening on NH_4^+ and NH_3 concentration can be expressed as follows.

$$\Delta\nu_A^* = S^+[NH_4^+] + C = S[NH_3] + C \quad (6)$$

The concentration of free NH_3 in the sample can be calculated from the usual relation

$$[NH_3] = K_A[NH_4^+]/a_H \quad (7)$$

where a_H is the hydronium ion activity and K_A is the dissociation constant for ammonium ion, corrected for temperature and ionic strength as described in the Experimental Section. A least-squares treatment of the line width *vs.* NH_4^+ and NH_3 concentration data (see Figure 4) gave the values of S^+ and S presented in Table IV.

The values of S^+ are quite reproducible for different experiments at one temperature, whereas the values for S are not nearly so reproducible. This reflects the fact that S depends on a precise knowledge of pH and the pK_A of ammonium ion. However, the fact that S (which contains information concerning the kinetics of the reaction of acetaldehyde with ammonia) *decreases* with increasing temperature is clear and will be considered further in the discussion.

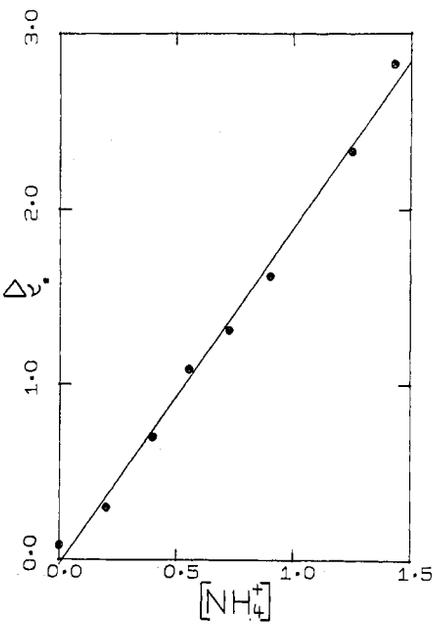


Figure 4.—Plot of residual line width for the acetaldehyde methyl doublet *vs.* ammonium ion concentration. Data are from sample set d_2 in Table IV, pH 7.0 at 10°.

TABLE IV

SLOPE OF ALDEHYDE METHYL LINE WIDTH *vs.* NH_4^+ AND NH_3 CONCENTRATION[a]

Temp, °C	pK_A[b]	Samples	S^+	S
10	9.730	d_1	1.87 ± 0.06	1710 ± 90
		d_2	1.91 ± 0.06	1580 ± 40
		e	1.95 ± 0.23	1270 ± 160
25	9.246	*e*	5.68 ± 0.17	1220 ± 40
34	8.976	*c*	4.37 ± 0.10	462 ± 8
		e	4.56 ± 0.08	522 ± 5

[a] Slopes are in units of Hz M^{-1} or l. mol^{-1} sec^{-1}. [b] pK_A of NH_4^+ at zero ionic strength (see Experimental Section). [c] 0.35 *M* CH_3CHO, 0.20 *M* NH_4Cl + KCl, 0.10 *M* phosphate, pH 7.00 at 25°. [d] 0.32 *M* CH_3CHO, 0.076 *M* CH_3CN, 1.60 *M* NH_4Cl + KCl, 0.10 *M* phosphate, pH 7.00 at 10°. [e] 0.40 *M* CH_3CHO, 0.063 *M* CH_3CN, 0.50 *M* NH_4Cl + KCl, 0.10 *M* phosphate, pH 7.00 at 10, 25, 34°.

In conjunction with the line broadening of acetaldehyde, we observed an upfield chemical shift of the aldehyde methyl doublet relative to acetonitrile while the hydrate showed no significant change in chemical shift. This change in chemical shift was found to be approximately linear in ammonia concentration, yielding a slope of 380 ± 20 Hz/mol of NH_3 which showed no observable dependence on temperature.

Discussion

Hydration of Acetaldehyde.—In much of the nmr work reported here it was necessary to calculate the concentrations of individual species present in the reaction mixtures. This was complicated by the fact that the adduct methyl resonances generally overlapped the hydrate resonance; hence, we often used the hydration equilibrium constant to calculate the hydrate concentration from that of the aldehyde.

Since kinetics of the addition of ammonia to acetaldehyde was studied by measuring the effect of ammonia on the line width of acetaldehyde, it was important to investigate whether any observed line broadening could

be due to an influence of ammonia on the hydration rate. The line width and hydration constant of acetaldehyde were found to be independent of NH_4^+ concentration at pH 4.8, while at pH 7–10 the aldehyde line width depends on NH_3 concentration. However, the line width of the hydrate is independent of NH_4^+ or NH_3. Thus, the line broadening of acetaldehyde in the presence of ammonia is due to a specific reaction with ammonia and not to a change in the hydration rate. The hydration reaction as an nmr chemical exchange problem has been studied in some detail.[23] Independent measurements of the hydration rate constant indicate that at neutral pH the contribution of exchange to the aldehyde and hydrate line widths would be negligible, in agreement with our observations.

Identity of the Ammonia Adducts.—The experiments which we have described demonstrate that at sufficiently high concentrations of NH_3 the major constituent present in ammoniacal solutions of acetaldehyde is the trimer 2,4,6-trimethylhexahydro-*s*-triazine. The formation of this trimer would be expected to proceed by a sequence of reactions whereby the addition of ammonia (or a primary amine) to the carbonyl group of acetaldehyde is followed by dehydration to form an imine, which undergoes further addition reactions. The detailed mechanism for the addition of RNH_2 to a carbonyl and subsequent imine formation has been demonstrated by several previous studies.[6,7b,24] A representative route to trimer from acetaldehyde and ammonia based on such a sequence is shown in Scheme I, where protonation equilibria have been omitted.

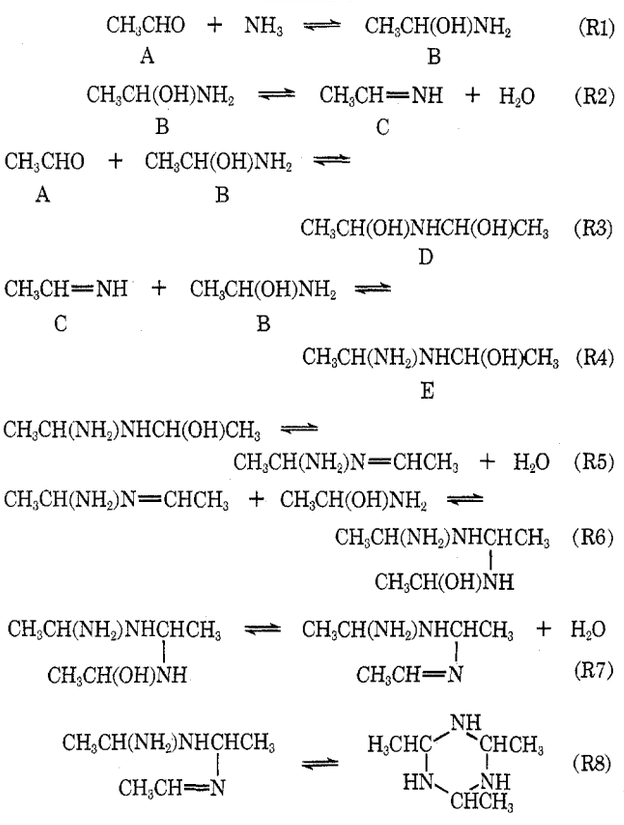
The accumulation of one or more of the intermediates or side products might be expected to occur under the appropriate conditions, and additional resonances were observed in the nmr spectra of aqueous solutions of acetaldehyde and ammonia (Figure 1, Table III). In addition to doublets corresponding to acetaldehyde hydrate and to trimer, three other methyl doublets could be identified when both acetaldehyde and ammonia were present. The doublets D_2 and D_3 were also observed in spectra of the commercial acetaldehyde–ammonia (Figure 2). Thus, these additional resonances represent intermediates involved in the equilibrium between the triazine trimer and free acetaldehyde and ammonia.

The effect of ammonia concentration and pH on the nmr spectra suggest that doublets 2 and 3 represent nonidentical methyl groups on the same molecular species, an amine with a $pK_A < 8$, while doublet 1 belongs to a compound with a single or equivalent methyl groups. The groups corresponding to D_1 and D_2 appear to be attached to a carbon containing one oxygen and one nitrogen as substituents, since the chemical shifts and coupling constants of these peaks are midway between the values for hydrate and trimer. On the other hand, methyl group D_3 would appear to be linked to a carbon bound to two nitrogens, since the coupling constant is the same as observed for the trimer and D_3 appears upfield of D_1 and D_2. We do not expect any

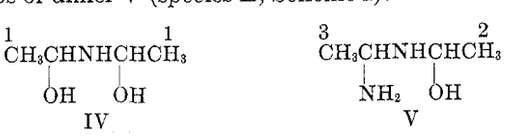
(23) M. L. Ahrens and H. Strehlow, *Discuss. Faraday Soc.*, **39**, 112 (1965); P. G. Evans, G. R. Miller, and M. M. Kreevoy, *J. Phys. Chem.*, **69**, 4325 (1965).

(24) (a) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **88**, 3367 (1966); (b) J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967); (c) J. Hine, J. C. Craig, J. C. Underwood II, and F. A. Via, *J. Amer. Chem. Soc.*, **92**, 5194 (1970).

SCHEME I



of the observed adducts to represent the carbinolamine 1-aminoethanol (see kinetic discussion to follow), and the various imines are probably too reactive to accumulate in a detectable amount. Furthermore, if these adducts were imines they would have detectable methyl resonances in the region near the aldehyde methyl where no additional peaks were observed. Based on the observed trends in chemical shift and coupling constant, and assuming that when a carbinolamine adds to a C=O or C=N group the nitrogen rather than the oxygen of the carbinolamine is the likely attacking nucleophile, we propose that the resonance D_1 belongs to the equivalent methyl groups of dimer IV (species D, Scheme I) while D_2 and D_3 belong to the two methyl groups of dimer V (species E, Scheme I).

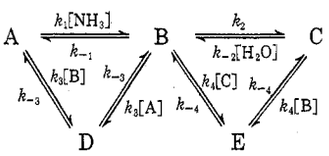


Kinetics of the Addition of Ammonia to Acetaldehyde.—The line broadening of the acetaldehyde methyl resonance in the presence of ammonia is the result of chemical exchange processes which place the methyl group in chemically and magnetically distinguishable environments. Since we have observed that acetaldehyde and the triazine trimer are in equilibrium, the methyl groups are exchanging among all species shown in Scheme I. However, the line broadening shown by the acetaldehyde methyl resonance depends only upon those exchange processes which contribute significantly to the lifetimes in solution of acetaldehyde and of the carbinolamine with which it is in direct equilibrium. We propose that reactions R1–R4 (Scheme I) are the most likely contributors to the lifetime of aldehyde.

The aldehyde–hydrate equilibrium need not be considered, since we have seen that under our experimental conditions this exchange is slow on the nmr time scale, resulting in no measurable line broadening effects. Furthermore, we have observed well-resolved resonances for the triazine trimer in solution, indicating that its decomposition is slow and is not important in determining the lifetime of aldehyde. Protonation equilibria will not be considered, since the rates involved are in the fast exchange-narrowed limit and the nmr resonances observed are the weighted average of the protonated and unprotonated forms.

The chemical exchange problem is summarized in Scheme II.

SCHEME II



Under these conditions the lifetime of species A may be expressed as

$$\frac{1}{\tau_A} = k_1[NH_3] + k_3[B] = (k_1 + k_3K_1[A])[NH_3] \quad (8)$$

where

$$K_1 = k_1/k_{-1} = \frac{[B]}{[A][NH_3]}$$

At this point it is useful to summarize our experimental observations. (1) The resonance corresponding to acetaldehyde (A) has a lorenztian line shape and the line width *increases linearly* with the concentration of NH_3. (2) The rate at which the line width increases (*i.e.*, the slope) *decreases* with increasing temperature from 10 to 35°. (3) The line width is independent of the concentration of acetaldehyde. (4) The chemical shift of acetaldehyde moves upfield linearly with NH_3 concentration. (5) At high NH_3 concentration we observe adducts with possible structures D and E (Scheme I).

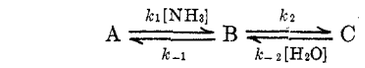
If steps R1 and R3 were in the slow exchange limit then the line width of A would be given by

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + \frac{1}{\tau_A} \quad (9)$$

From eq 8 it is seen that the line width would vary linearly with $[NH_3]$ and also should show a linear dependence on [A]. However, our observations suggest that the term containing [A] does not contribute in a measurable amount to the lifetime of A. This slow exchange result could only show a negative temperature dependence if the term containing K_1 was significant. In the typical slow exchange case the chemical shift of A is expected to remain fixed until line broadening becomes substantial. However, we have observed consistent chemical shifts with line broadening of only 1–3 Hz. Thus, our observations are inconsistent with the slow exchange situation represented by eq 8 and 9.

We have previously described the observation of adducts for which we propose the dimeric structures corresponding to species D and E. Since these species have nearly equal chemical shifts their interconversion must be quite slow (steps 3 and 4), indicating that these species have little effect on the lifetime of the aldehyde. Furthermore, the involvement of D necessitates a dependence of the lifetime of A on the concentration of A, which we did not observe. Therefore, based on the evidence at hand, we reduce the chemical exchange problems to three sites (Scheme III).

SCHEME III



At pH 7 with $[NH_3] \sim 10^{-4}$–10^{-3} M we expect that the concentration of carbinolamine (B) and imine (C) will be much less than the concentration of aldehyde. In the Appendix we present the general solution (originally developed by Swift and Connick[25]) for the three-site exchange problem under these conditions where A is the dominant species.

From eq A2 and A3 (see Appendix) the line width and chemical shift of acetaldehyde are given by

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1[NH_3]\left[1 - \frac{k_{-1}\tau_B}{1 + \tau_B^2\Delta\omega_{BC}^2}\right] \quad (10)$$

$$\omega_{obsd} - \omega_A = -K_1[NH_3]\left[\frac{k_{-1}^2\tau_B^2}{1 + \tau_B^2\Delta\omega_{BC}^2}\right]\Delta\omega_{BC} \quad (11)$$

where

$$\frac{1}{\tau_B} = \frac{1}{T_{2B}} + k_{-1} + \epsilon k_2 \quad (12)$$

$$\Delta\omega_{BC} = \Delta\omega_b + \gamma\frac{K_2}{[H_2O]}\Delta\omega_c \quad (13)$$

$$\epsilon = \frac{1/T_{2c}^2 + k_{-2}[H_2O]/T_{2c} + \Delta\omega_c^2}{(1/T_{2c} + k_{-2}[H_2O])^2 + \Delta\omega_c^2} \leq 1 \quad (14)$$

$$\gamma = \frac{1}{(1 + 1/T_{2c}k_{-2}[H_2O])^2 + (\Delta\omega_c/k_{-2}[H_2O])^2} \leq 1 \quad (15)$$

The expressions for τ_B and $\Delta\omega_{BC}$ are independent of $[NH_3]$; hence, the line width and chemical shift should vary linearly with ammonia concentration regardless of the rate constants involved.

If the lifetime of the carbinolamine were in a slow exchange limit where $\tau_B^2\Delta\omega_{BC}^2 \gg 1$, then the line width would reduce to

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1[NH_3] \quad (16)$$

Under these conditions the line width would be expected to increase with increasing temperature owing to an increase in the rate k_1, a situation which is not compatible with our results.

According to eq 10, the line width will decrease with increasing temperature only if the term in brackets (containing τ_B) has a negative temperature dependence which exceeds the positive dependence of k_1. Rearranging eq 10 gives

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1\left[\frac{\tau_B^2\Delta\omega_{BC}^2 + \dfrac{\epsilon k_2 + 1/T_{2B}}{k_{-1} + \epsilon k_2 + 1/T_{2B}}}{1 + \tau_B^2\Delta\omega_{BC}^2}\right][NH_3] \quad (17)$$

For fast exchange, where $\tau_B^2\Delta\omega_{BC}^2 \ll 1$, the line width will have a negative temperature dependence, since $k_1\tau_B^2$ will have the temperature dependence of τ_B, and k_1 multiplied by the second term in brackets can be shown always to have a negative temperature de-

(25) T. J. Swift and R. E. Connick, *J. Chem. Phys.*, **37**, 307 (1962).

pendence. Thus our results indicate that we are dealing with a fast exchange situation. We therefore cannot observe a distinct resonance for the carbinolamine, since the "aldehyde" resonance is actually the coalesced resonance for both species. Using the fast exchange condition $\tau_B^2\Delta\omega_{BC}^2 \ll 1$ and the fact that $k_{-1} + \epsilon k_2 \gg 1/T_{2B}$ ($1/T_{2B} \sim 1$ sec^{-1}), eq 17 and 11 may be expressed as follows

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1\left[\tau_B^2\Delta\omega_{BC}^2 + \frac{\epsilon k_2 + 1/T_{2B}}{k_{-1} + \epsilon k_2}\right][NH_3]$$
$$= \pi(S[NH_3] + C) \quad (18)$$

$$\omega_{obsd} - \omega_A = -K_1\left(\frac{k_{-1}}{k_{-1} + \epsilon k_2}\right)^2\Delta\omega_{BC}[NH_3] \quad (19)$$

where S is the slope of a plot of $\Delta\nu_A$* *vs.* $[NH_3]$ (Table IV).

The term $\Delta\omega_{BC}$ as defined by eq 13 consists of two parts. The quantity $\Delta\omega_b = \omega_{obsd} - \omega_b$ can be estimated as $\sim 2\pi$ (90 Hz) from the fact that the carbinolamine is expected to have a chemical shift very near that of the hydrate. The second term $\gamma\cdot(C/B)\Delta\omega_C$ is more difficult to estimate. However, nmr data for imines suggest that $\Delta\omega_C \lesssim 2$ (20 Hz) and we do not expect $\gamma\cdot(C/B)$ to be large, since $C/B = k_2/k_{-2}[H_2O]$ and if $k_{-2}\cdot[H_2O] < \Delta\omega_C$ then $\gamma \ll 1$. Thus reasonable limits for $\Delta\omega_{BC}$ are

$$550 \leqslant \Delta\omega_{BC} \leqslant 1000 \quad (20)$$

By analogy with data from other systems it is reasonable to assume $\epsilon k_2 \lesssim k_{-1}$. Using this constraint and those described above, limits for the kinetic parameters for carbinolamine formation can be derived. First, the fast exchange condition $\tau_B^2\Delta\omega_{BC}^2 \ll 1$ implies that $k_{-1} + \epsilon k_2 > 550$ or $k_{-1} \gtrsim 300$ sec^{-1}. Next considering eq 18, the term in brackets will be $\gtrsim 1/2$ so that $k_1 \gtrsim 2\pi\cdot S$. From the values of S at 10° (Table IV) $k_1 \gtrsim 10^4\ M^{-1}$ sec^{-1}. Finally we have found that a plot of the aldehyde chemical shift *vs.* $[NH_3]$ has a slope of 380 Hz M^{-1}. From this result and eq 19 and 20, upper and lower bounds for K_1 can be determined. The kinetic parameters are summarized below.

$$k_{-1} > 3 \times 10^2 \text{ sec}^{-1} \qquad k_1 \gtrsim 10^4\ M^{-1}\text{ sec}^{-1}$$
$$2 \lesssim K_1 \lesssim 17\ M^{-1} \quad (21)$$

For comparison, Hine, *et al.*,[24c] have determined the individual rate constants for the reaction of methylamine with isobutyraldehyde. Their values are $k_1 \sim 5 \times 10^5\ M^{-1}$ sec^{-1}, $k_2 \sim 40$ sec^{-1}, and $K_1 = 8.5\ M^{-1}$ at pH 7 and 35°. Hine and Via[8] also found that for a series of alkylamines with polar substitutents K_1 shows a good linear correlation with pK_a and the Taft steric constant E_s. From their relation we calculate a K_1 for ammonia of $\sim 4\ M^{-1}$, a value within the range determined by nmr. (This agreement may be fortuitous, however, since it may be argued that ammonia cannot be treated as a primary amine.) Finally, Hine and Kokesh[26] used nmr to study the addition of trimethylamine to formaldehyde, finding that, at 25°, $k_1 = 1.3 \times 10^7\ M^{-1}$ sec^{-1} and $k_{-1} = 3.4 \times 10^3$ sec^{-1}.

Ogata and Kawasaki[27] studied the kinetics of the addition of ammonia to acetaldehyde by following the decrease in the carbonyl absorption at 278 nm. For calculating rate and equilibrium constants, they assumed that no adducts other than the carbinolamine were formed. However, our results indicate that their experimental conditions of high pH, low temperature, and reactant concentrations of 0.1 M would lead to a substantial amount of other adducts, including the triazine trimer. Furthermore, their rate constants are too low ($k_1 = 26\ M^{-1}$ sec^{-1} at 5°, pH 7) to account for the observed nmr line broadening. We believe that these workers were actually observing the rate-determining step(s) in the slow overall conversion of acetaldehyde to trimer.

Experimental Section

Reagents.—Practical grade acetaldehyde (Matheson Coleman and Bell) was distilled at room temperature immediately prior to use. Nmr observations showed that aqueous solutions of acetaldehyde so purified were free of 1,1′-oxydiethanol,[28] paraldehyde, and acetic acid under all of our experimental conditions. Spectrograde acetonitrile was obtained from Eastman. Analytical reagent grade KCl, NH_4Cl, KH_2PO_4, and K_2HPO_4 were desiccated and used without further purification.

2,4,6-Trimethylhexahydro-*s*-triazine.—Technical grade acetaldehyde–ammonia from Eastman was purified by sublimation at 3 mm, maintaining sample temperature at 40–45° and condensing the sublimate on a cold finger at 5°. Large white crystals of 2,4,6-trimethylhexahydro-*s*-triazine were obtained free from water of hydration (mp 95–96°).

Mass spectra were obtained on an Associated Electrical Industries MS-9 instrument; the parent peak at m/e 129 and extensive fragmentation pattern observed were consistent with the formula $(CH_3CHNH)_3$. Infrared spectra were obtained on a Perkin-Elmer Infracord, and samples were prepared as mulls in Kaydol mineral oil and hexachlorobutadiene.

Sample Preparation.—All samples were prepared fresh and kept cold prior to nmr observations. Aldol condensation was not observed to take place during the course of the experiment, although high pH samples did turn yellow after several hours at room temperature. The sample pH was measured using a Beckman Expandomatic pH meter and 39030 combination electrode; adjustments of pH were made using 6 M HCl or concentrated KOH solutions. A water bath maintained samples within ±2° of the desired temperature throughout the period of measurement and adjustment.

Nmr Spectroscopy.—Proton nmr spectra were obtained at 100 MHz on a Varian HA-100D spectrometer equipped with a variable-temperature probe. A line width and chemical shift reference (acetonitrile) was added to each sample and for aqueous solutions the H_2O resonance was used as a field–frequency lock. Using a flow of nitrogen gas through a Dry Ice–acetone heat exchanger, sample temperatures could be maintained to ±0.2°. Actual temperatures were determined from the chemical shift of the OH resonance in a methanol reference sample using the calibration results of Van Geet.[29]

Spectra were taken using 50-Hz sweep widths and sweep rates of 0.05 or 0.02 Hz/sec. The observed RF power levels were maintained below saturation. Line widths were measured relative to the reference peak whose line width is dominated by field inhomogeneity and is independent of pH or other species present. Chemical shifts were measured with the Hewlett-Packard frequency counter for the HA-100 and are believed accurate to ±0.2 Hz (±0.002 ppm).

Concentration Determination.—Areas under peaks were measured with a Keuffel and Esser Model 620005 polar planimeter, and the individual peak areas were normalized by dividing by the total area for all methyl groups. Concentrations of individual species were calculated by assuming that the total methyl area was equivalent to the initial acetaldehyde concentration. Overlap of the hydrate methyl by other adducts made its measurements difficult; therefore, the concentration of hydrate was usually calculated from the aldehyde peak using the hydration equilibrium constant. The concentration of NH_4^+ plus NH_3 was calculated

(26) J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970).

(27) Y. Ogata and A. Kawasaki, *Tetrahedron*, **20**, 855 (1964); Y. Ogata and A. Kawasaki, *ibid.*, 1573 (1964).

(28) G. Socrates, *J. Chem. Soc., Chem. Commun.*, 702 (1969); F. Podo and V. Viti, *Org. Magn. Resonance*, **3**, 259 (1971).

(29) A. L. Van Geet, *Anal. Chem.*, **42**, 679 (1970).

by subtracting from the initial concentration the amount of ammonia incorporated into adduct, assuming one ammonia incorporated per adduct methyl group.

The pK_A of Ammonium Ion.—The pK_A of ammonium ion has been found to satisfy the following equation at 25°.[30]

$$pK_A = pK_A^\circ + 0.132[NH_4Cl] + 0.198[KCl] \quad (22)$$

The value of pK_A° is obtained from the data of Bates and Pinching,[31] who determined pK_A as a function of temperature and extrapolated to zero ionic strength.

$$pK_A^\circ = 2835.75/T - 0.6322 + 0.001225T \quad (23)$$

The variation of mean activity coefficients with temperature over the range of 10–35° has been found to be at most 4% at 2 *m* concentration.[32] Therefore, we have used eq 22 over this temperature range with the appropriate pK_A° determined by eq 23. Any specific effect of the phosphate buffer was not considered.

Appendix

The interpretation of the nmr line broadening results for acetaldehyde in the presence of ammonia depends upon the relationship between chemical exchange and nmr line shapes. From the arguments presented in the text, the system involves exchange among three chemically distinguishable sites.

$$A \underset{1/\tau_{ba}}{\overset{1/\tau_{ab}}{\rightleftharpoons}} B \underset{1/\tau_{cb}}{\overset{1/\tau_{bc}}{\rightleftharpoons}} C \quad (A1)$$

The dependence of nmr line shape on chemical exchange can be analyzed with the standard classical Bloch equations. This treatment is valid in the present system, in which intact methyl groups and methine protons are exchanging among different chemical species.[33] Below are presented the general equations describing the behavior of the chemical shift and line width of the A resonance in the presence of chemical exchange when [A] ≫ [B], [C]. These equations are expressed in the form most useful for the analysis of the system under study.

$$\pi\Delta\nu_A = \frac{1}{T_{2a}} + \frac{1}{\tau_{ab}}\left[1 - \frac{\tau_B/\tau_{ba}}{1 + \tau_B^2\Delta\omega_{BC}^2}\right] \quad (A2)$$

$$\omega_{obsd} - \omega_A = -\frac{[B]}{[A]}\left[\frac{\tau_B^2/\tau_{ba}^2}{1 + \tau_B^2\Delta\omega_{BC}^2}\right]\Delta\omega_{BC} \quad (A3)$$

$$\frac{1}{\tau_B} \equiv \frac{1}{T_{2b}} + \frac{1}{\tau_{ba}} + \frac{\epsilon}{\tau_{bc}} \quad (A4)$$

$$\Delta\omega_{BC} \equiv \Delta\omega_b + \gamma\frac{[C]}{[B]}\Delta\omega_c \quad (A5)$$

$$\epsilon = \frac{1/T_{2c}^2 + 1/T_{2c}\tau_{cb} + \Delta\omega_c^2}{(1/T_{2c} + 1/\tau_{cb})^2 + \Delta\omega_c^2} \leq 1 \quad (A6)$$

$$\gamma = \frac{1}{\left(1 + \frac{\tau_{cb}}{T_{2c}}\right)^2 + \tau_{cb}^2\Delta\omega_c^2} \leq 1 \quad (A7)$$

The line width $\Delta\nu_A$ as usually defined is the full width at half height; ω_i and T_{2i} are the chemical shift (in rad/sec) and the spin–spin relaxation time (in seconds) for the site i in the absence of exchange; ω_{obsd} is the observed chemical shift for site A in the presence of exchange; $\Delta\omega_i = \omega_{RF} - \omega_i \approx \omega_{obsd} - \omega_i$, where ω_{RF} is the frequency of the swept RF field. The terms τ_B, which can be considered a generalized lifetime for site B, and $\Delta\omega_{BC}$, a generalized chemical shift, have been defined to reduce the complexity of the expressions A2 and A3, resulting a in pseudo-two-site formalism.

Registry No.—Acetaldehyde, 75-07-0; ammonia, 7664-41-7; 2,4,6-trimethylhexahydro-*s*-triazine, 638-14-2; acetaldehyde hydrate, 4433-56-1.

(30) M. T. Emerson, E. Grunwald, and R. A. Kromhout, *J. Chem. Phys.*, **33**, 547 (1960).
(31) R. G. Bates and G. D. Pinching, *J. Amer. Chem. Soc.*, **72**, 1393 (1950).
(32) H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 727.
(33) H. M. McConnell, *J. Chem. Phys.*, **28**, 430 (1958).

Heterocyclic Studies. 39. Enolic and Bicyclic Isomers of 2,3- and 1,5-Dihydro-1,2-diazepin-4-ones[1]

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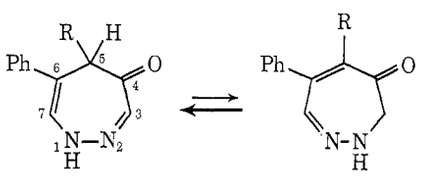
Received December 12, 1972

Conditions are described for conversion of the 1,5- and 2,3-dihydrodiazepinones **1** and **2** to *N*-acyl ketones and to *N*-acylenol esters. Enol acylation is much more rapid in the 1,5-dihydro series. Acylation of the 1,5-dihydrodiazepinones under conditions favoring N-2 substitution leads to 2-acyl-2,3-diazabicyclo[3.2.0]-3-heptenones. These bicyclic ketones lose the elements of methylketene or phenylketene on heating, giving 1-acyl-4-phenylpyrazoles.

In an earlier note we reported the formation of the 1,5-dihydrodiazepinone **1a** by base-catalyzed isomerization of the 2,3-dihydro tautomer **2a**.[2] Interconversion of these ketones involves an equilibrium of the respective enolates in which the 1,5-dihydro isomer predominates (**1a**:**2a** ~8). This approach has been applied also to the 2,3-dihydro-5,6-diphenyldiazepinone **2b**,[3] and provided the 1,5-dihydro tautomer **1b** in about 50% yield. The position of the equilibrium could not be measured as was done in the 5-methyl series because of the lack of a distinctive nmr signal, but it clearly favors the 1,5-dihydro tautomer.



1,5-dihydro 2,3-dihydro

1a, R = CH_3 **2a**, R = CH_3
b, R = C_6H_5 **b**, R = C_6H_5

Both of these diazepinone systems contain a multiplicity of nucleophilic centers. In the 2,3-dihydro series, substitutions at N-1, N-2, and C-3 have been observed. Highly reactive electrophiles such as acid chlorides and oxonium reagents attack **2a** at the N-1 position, leading in the former case to the bicyclo-

(1) Supported in part by grants from the National Science Foundation and the Unidel Foundation.
(2) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 1369 (1968). Complete details of these base-catalyzed reactions will be found in the Ph.D. Dissertation of M. G. Pleiss, University of Delaware, 1969.
(3) A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970).