(6.8 mm) [lit.[13,14] 115–117° (1 mm), 107–109° (0.3–0.7 mm)]; ir (neat) 1950 (C=C=C) cm^{-1}.

1-Chloro-1,3-diphenyl-4,4-dimethyl-1,2-pentadiene (Id) was prepared according to the procedure reported earlier.[2,14] Distillation gave a 60% yield of the chloroallene, bp 130–131° (1 mm) [lit.[14,19] 145–147° (2–3 mm)]; ir (neat) 1920 (C=C=C) cm^{-1}; nmr (CCl_4) δ 1.25 (s, 9) and 7.3 (m, 10).

1-Chloro-1-phenyl-3-*tert*-butyl-4,4-dimethyl-1,2-pentadiene (Ie) was prepared in the above manner. Distillation afforded 62% of the desired chloroallene, bp 76–77° (0.3 mm); ir (neat) 1960 (C=C=C) cm^{-1}; nmr (CCl_4) δ 1.15 (s, 9), 1.30 (s, 9), 7.15 (m, 5).

Anal. Calcd for $C_{17}H_{23}Cl$: C, 77.71; H, 8.76; Cl, 13.52. Found: C, 77.77; H, 8.80; Cl, 13.51.

3-Chloro-1,1-diphenyl-4,4-dimethyl-1,2-pentadiene (If) was prepared as above in 80% yield, mp 37–40° (crystallized at −78° from ether); ir (CCl_4) 1945 (C=C=C) cm^{-1}.

Anal. Calcd for $C_{19}H_{19}Cl$: C, 80.71; H, 6.72; Cl, 12.57. Found: C, 80.56; H, 6.82; Cl, 12.67.

Product Studies. A 1-g sample of the chloroallene was transferred to 1 l. of an aqueous acetone solution thermostated at 35–55° depending upon the rate of solvolysis expected. After ten half-lives, 500 ml of distilled water was added and saturated with NaCl and the resulting solution extracted with five 200-ml portions of ether. The organic layer was dried over $MgSO_4$ and evaporated. Table III lists the spectral data obtained for each product study along with the nmr analysis of product mixtures when formed.

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Primary Amine Catalysis in the Dealdolization of Diacetone Alcohol

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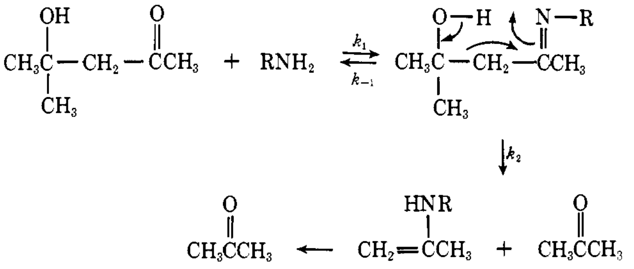
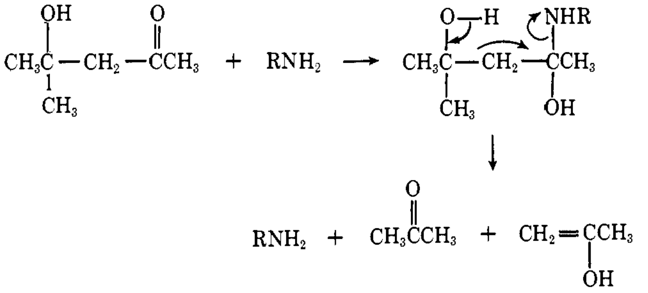
Abstract: The *n*-propylamine-catalyzed dealdolization of diacetone alcohol has been studied over the pH range 9.9–12.7 at 25°. The overall rate of reaction depends on a group with a pK_a of 10.9 which is assigned to the amine. The existence of a ketimine intermediate has been confirmed by direct spectral observation. This intermediate is formed rapidly and reversibly ($K = 0.15\ M^{-1}$) from *n*-propylamine and diacetone alcohol, with subsequent decomposition in a slow step to give product acetone. An observed solvent isotope effect ($k_{H_2O}/k_{D_2O} = 1.8$) is dissected into a contribution due to the formation of the ketimine ($K_{H_2O}/K_{D_2O} = 1.3$) and an effect on the breakdown of the intermediate ($k_{H_2O}/k_{D_2O} = 1.4$). The small isotope effect on the breakdown indicates that proton transfer is probably not occurring in the transition state. The solvent effect on the decomposition of the ketimine is likewise small ($k_{H_2O}/k_{80\%\ \mathrm{ethanol}} = 8$) which suggests that the transition state is only slightly polar.

The catalysis of dealdolization reactions by primary amines is of considerable interest as a model for enzymatic aldol condensation since it has been shown that the terminal amino group of a lysine residue is covalently involved in the action of many of these enzymes.[1] The much greater effect of primary amines than secondary amines as catalysts for this reaction (tertiary amines are inactive) suggests[2] the involvement of a ketimine intermediate which decomposes to a molecule of acetone plus an enamine. Similar mechanisms have been postulated[3] for both enzymatic and nonenzymatic decarboxylations of β-keto acids.



Recently, it has been proposed[4] that primary amine catalysis of the dealdolization of diacetone alcohol may actually involve the intermediate formation of a reactive carbinolamine rather than a ketimine. This proposal was based primarily on extrapolations of data on rates of formation of ketimines which indicated that the rate of formation of a ketimine would be too slow to account for the observed catalysis.



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[1] (a) B. L. Horecker, S. Pontremli, C. Ricci, and T. Cheng, *Proc. Nat. Acad. Sci. U. S.*, **47**, 1949 (1961); (b) E. Grazi, P. T. Rowley, T. Cheng, O. Tchol, and B. L. Horecker, *Biochem. Biophys. Res. Commun.*, **9**, 38 (1962); (c) for a general review of the mechanism of action of aldolases see D. E. Morse and B. L. Horecker, *Advan. Enzymol. Rel. Subj. Biochem.*, **31**, 125 (1968).

[2] F. H. Westheimer and H. Cohen, *J. Amer. Chem. Soc.*, **60**, 90 (1938).

[3] (a) G. A. Hamilton and F. H. Westheimer, *ibid.*, **81**, 6332 (1959); (b) S. Warren, B. Zerner, and F. H. Westheimer, *Biochemistry*, **5**, 817 (1966); (c) K. J. Pederson, *J. Phys. Chem.*, **38**, 559 (1934); *J. Amer. Chem. Soc.*, **60**, 595 (1938).

[4] R. W. Hay and K. R. Tate, *Aust. J. Chem.*, **19**, 1651 (1966).

The present work was undertaken to determine (1) if a ketimine intermediate is formed rapidly enough to be involved in the catalytic process; (2) if it is, whether the formation or decomposition of this intermediate is rate determining; (3) what the nature of the transition state is for this reaction; and (4) whether this type of catalysis can explain a large portion of the catalytic efficiency of the aldolase enzymes.

The choice of *n*-propylamine as the catalyst is due to its obvious resemblance to the side chain of lysine.[5]

Experimental Section

Materials. Commercial diacetone alcohol showed a peak in the ultraviolet spectrum at 243 nm (apparent extinction coefficient of 86, which corresponds to about 0.5% mesityl oxide impurity). The material was purified by distillation through a spinning band column at about 20 mm. Later fractions could be obtained with about 0.03% mesityl oxide impurity, but further distillation of these fractions resulted in an increase of impurity, probably due to thermal loss of water.

n-Propylamine was reagent grade and was distilled before use. Buffer solutions were made up by weighing a quantity of amine in a volumetric flask and adding standardized 1.0 *N* HCl, potassium chloride, and distilled water to give the appropriate pH, and μ = 0.2.

Deuterium oxide was obtained from Bio-Rad and was 99.8% D. Solutions in D_2O were made up by dissolving deuterated amine in D_2O and adding the appropriate amount of *ca.* 38% DCl in D_2O (99% D, Stohler Isotope Chemicals). The deuterated amine was prepared by dissolving the amine in D_2O and distilling the amine. The final *n*-propylamine-d_2 was *ca.* 90% deuterated on the nitrogen and showed no impurities on gas chromatographic analysis.

Kinetic Methods. All kinetic measurements were carried out at 25.0 ± 0.2° and ionic strength of 0.2 made up with KCl. At the lower pH values studied, the pH was kept constant by using the amine and amine hydrochloride system itself as a buffer. At higher pH's potassium hydroxide was added where necessary to adjust the pH. The pH was measured at the end of each kinetic run and any run showing a deviation of greater than 0.04 pH unit from the mean was discarded. pH measurements were made with a Radiometer pH meter Type 26. pD values were calculated from the equation pD = pH + meter reading + 0.4.[7]

Rates were followed using either a Gilford 2000 or 2400 spectrophotometer. The production of acetone from diacetone alcohol was monitored at 260 nm at a concentration of diacetone alcohol of about 1.4×10^{-2} *M*. The total change in absorbance was of the order of 0.2. The formation of the ketimine from diacetone alcohol and *n*-propylamine was measured at 235 nm by rapidly adding 30.0 μl of diacetone alcohol to 3.00 ml of solution of the amine buffer and observing the increase in absorbance.

The kinetics were analyzed by a nonlinear least-squares regression analysis program written for a Wang Model 700 programming calculator by Dr. Hyman of this department. These rate constants were then plotted *vs.* the concentration of amine at constant pH, and the slope and intercept obtained by use of a weighted least-squares program, with each point weighted by the reciprocal of the square of the rate constant. Justification for this procedure is found in the fact that, if one assumes that the per cent error in each of the rate constants is a constant, then each point is weighted proportional to its variance, as suggested by Bacon.[8]

The pH–rate profiles were analyzed by using the weighted least-squares program on the form of the rate eq 1. In the analysis of the pH–rate profile in D_2O, all of the observed rate constants were used, but in the analysis of the pH–rate profile in H_2O, only those rate constants below pH 12 were used. This procedure was followed because the three rate constants at highest pH all had quite large standard deviations (15–20%). Inclusion of these points in the calculation gives a value of k^{lim} which is about 20% lower than without these points. However the two values of k^{lim} agree within their respective standard deviations.

$$\frac{1}{k^{\mathrm{obsd}}} = \frac{1}{k^{\mathrm{lim}}} + \frac{a_{\mathrm{H}^+}}{k^{\mathrm{lim}}K_{\mathrm{a}}} \qquad (1)$$

pK_a's were measured under the same conditions as the kinetics by measuring pH values at various buffer ratios ranging from 1:10 to 10:1 for the water solutions and from 1:3 to 3:1 for the deuterium oxide solutions. pK_a's were calculated for each buffer concentration and the results averaged.

Equilibrium constants for the formation of the ketimine intermediate were measured spectrophotometrically. The method used was a modification of that of Williams and Bender.[9] The formation of the ketimine was monitored at 235 nm and the change in absorbance due to this reaction was obtained from the computer output. This value was converted to a concentration by using an assumed extinction coefficient[9] of 1.92×10^2. Equilibrium constants were then calculated in the usual manner with the assumption that there is no change in diacetone alcohol concentration.

Results

The dealdolization of diacetone alcohol (4-hydroxy-4-methyl-2-pentanone) may be followed by monitoring the change in absorbance at 260 nm due to product acetone. In order to follow the reaction spectrally, however, it is first necessary to rigorously purify the material since commercial diacetone alcohol is contaminated with the strongly absorbing mesityl oxide ($\lambda_{\max}$ 243, ϵ 1.4×10^4) which also undergoes reaction with amines, obscuring the primary reaction.[10] We were able to purify the diacetone alcohol by spinning band distillation to a point where the change in absorbance due to the mesityl oxide impurity amounted to less than 10% of the total change in absorbance (less than 0.05% mesityl oxide impurity). Since the reaction of *n*-propylamine with mesityl oxide is substantially faster than from the production of acetone,[10] we were able to obtain good rate constants simply by ignoring the first few per cent of the reaction.

The observed rates of ketimine formation were not appreciably affected by the presence of trace mesityl oxide since the formation of ketimine from diacetone alcohol is more rapid than the reaction of amine with mesityl oxide. The change in absorbance due to impurity is less than 5% of the total change in absorbance under the conditions used to monitor the reaction.

All reactions were followed through at least three half-lives; stable infinity points were generally obtained; and the final uv spectrum was that of acetone over the entire measurable range (230–350 nm). Runs were made at 25.0 ± 0.2° at an ionic strength of 0.2 *M* made up with KCl. The initial concentration of diacetone alcohol was 1.4×10^{-2} *M* and the total amine concentration ranged from about 0.05 to 0.4 *M*.

Rate constants for the amine-catalyzed reaction were determined from a weighted least-squares analysis of plots of k^{obsd} *vs.* total amine concentration at constant pH. These rate constants are given in Table I. Intercepts of these plots gave the rate constants for the hydroxide-catalyzed rate of dealdolization which were $k_{\mathrm{OH}^-} = 6.3 \pm 0.7 \times 10^{-3}$ M^{-1} sec^{-1} and $k_{\mathrm{OD}^-} = 1.26 \pm 0.17 \times 10^{-2}$ M^{-1} sec^{-1}, giving a solvent isotope effect of 2.0 ± 0.3. These values agree well with pre-

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[5] The use of the amino group in *n*-propylamine as a model for the one of the lysine at the active site of aldolase may not be valid since it has recently been reported[6] that in the related enzyme acetoacetate decarboxylase the analogous lysine residue has a pK_a of about 6. This value is substantially lower than the pK_a of *n*-propylamine which is about 11.

(6) (a) D. E. Schmidt, Jr., and F. H. Westheimer, *Biochemistry*, 10, 1249 (1971); (b) F. H. Westheimer, presented at the 23rd Congress of the International Union of Pure and Applied Chemistry, Boston, Mass., July 1971; (c) F. C. Kokesh and F. H. Westheimer, *J. Amer. Chem. Soc.*, **93**, 7270 (1971).

(7) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

(8) R. H. Bacon, *Amer. J. Phys.*, 21, 428 (1953).

(9) A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2508 (1966).

(10) R. M. Pollack and D. Strohbeen, *ibid.*, **94**, 2534 (1972).

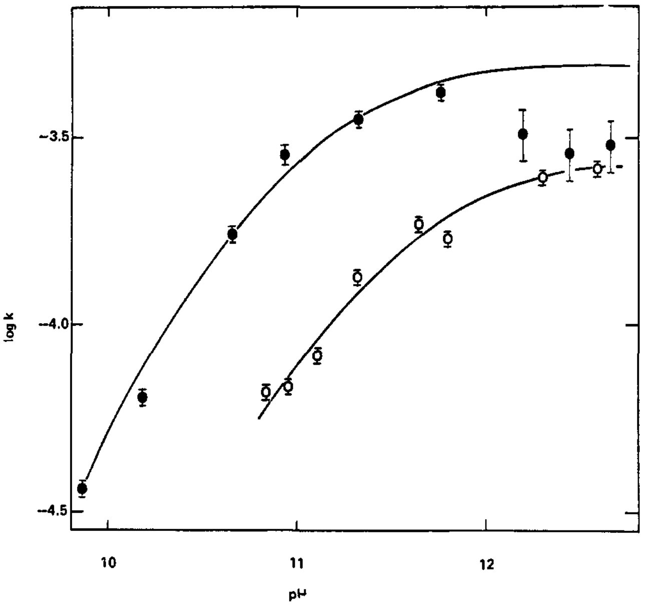

Figure 1. Rate–acidity profile for the dealdolization of diacetone alcohol catalyzed by *n*-propylamine at 25.0°. Closed circles are for water and open circles are D_2O.

Table I. Rate of *n*-Propylamine Catalysis of Dealdolization of Diacetone Alcohol at 25°

No. of points	pH	k, M^{-1} sec^{-1} [a]	Log k
2	9.93	$3.96 \pm 0.15^b \times 10^{-5}$	−4.40
4	10.18	$6.40 \pm 0.10 \times 10^{-5}$	−4.19
4	10.66	$1.76 \pm 0.03 \times 10^{-4}$	−3.76
4	10.92	$2.81 \pm 0.15 \times 10^{-4}$	−3.55
4	11.34	$3.50 \pm 0.11 \times 10^{-4}$	−3.46
4	11.77	$4.25 \pm 0.06 \times 10^{-4}$	−3.38
5	12.19	$3.28 \pm 0.46 \times 10^{-4}$	−3.49
6	12.44	$2.68 \pm 0.56 \times 10^{-4}$	−3.54
4	12.67	$2.92 \pm 0.60^b \times 10^{-4}$	−3.54
	pD		
4	10.82	$6.8 \pm 1.0 \times 10^{-5}$	−4.17
4	10.92	$7.10 \pm 0.21 \times 10^{-5}$	−4.15
4	11.08	$8.98 \pm 0.62 \times 10^{-5}$	−4.06
3	11.32	$1.35 \pm 0.03 \times 10^{-4}$	−3.87
3	11.65	$1.81 \pm 0.06 \times 10^{-4}$	−3.75
4	11.78	$1.66 \pm 0.14 \times 10^{-4}$	−3.78
3	12.30	$2.52 \pm 0.17 \times 10^{-4}$	−3.60
3	12.56	$2.79 \pm 0.03 \times 10^{-4}$	−3.56

[a] Errors are standard deviations. [b] Errors are estimated.

viously published values from dilatometric measurements, *e.g.*, $k_{OH^-} = 7.37 \times 10^{-3}$ M^{-1} sec^{-1} [4] and $k_{OD^-}/k_{OH^-} = 1.45$.[11] It should be noted in this context that the values of rate constants that we obtain for the hydroxide and deuterioxide catalyzed reactions are based on activity of hydroxide ion rather than concentration, so that our rate constants are not strictly comparable to previous results.

The rate constants for amine catalysis in water and deuterium oxide can be correlated with eq 2. The

$$k = k^{\text{lim}}K_a/(\alpha_H + K_a) \tag{2}$$

values of the calculated parameters are $k_{H_2O}{}^{\text{lim}} = 4.95 \pm 0.53 \times 10^{-4}$ M^{-1} sec^{-1}, $k_{D_2O}{}^{\text{lim}} = 2.75 \pm 0.29 \times 10^{-4}$ M^{-1} sec^{-1}, $pK_a{}^{H_2O} = 10.9 \pm 0.06$, $pK_a{}^{D_2O} = 11.35 \pm 0.06$. The data are plotted in Figure 1; the curve is the theoretical one using the calculated constants. The rate constants above pH 12 were not used in the calculation of the theoretical line since they have large standard deviations. In addition, at high pH, the hydroxide ion catalyzed rate becomes a major fraction of the observed rate and a slight medium effect due to added amine on the hydroxide ion rate would have a marked effect on the calculated rate constant for amine catalysis.[12] pK_a's of *n*-propylamine in both water and deuterium oxide were measured under the conditions used for the kinetics and found to be 10.90 ± 0.04 and 11.43 ± 0.04 (lit. value for *n*-propylamine in water is 10.53),[14a] in good agreement with the kinetically determined pK_a's.

The formation of an intermediate could be observed spectrally at 235 nm. Equilibrium constants for this reaction were measured under various conditions of pH and amine concentration, with the diacetone alcohol concentration constant at 0.08 *M*. Calculated values for water ([amine] = 0.399 *M*) are 0.153 ± 0.005 M^{-1} at pH 10.86 and 0.156 ± 0.001 M^{-1} at pH 11.75 (equilibrium constants do not include [H_2O]). Corresponding calculations in D_2O at pD's of 11.34 to 11.91 give $K_D = 0.114 \pm 0.012$ making the isotope effect on the equilibrium $K_H/K_D = 1.34 \pm 0.13$. To insure the independence of K_H on amine concentration, measurements were made at pH 10.86 and amine concentrations of 0.0638 and 0.266 *M*. These gave equilibrium constants in water of 0.140 ± 0.017 M^{-1} and 0.145 ± 0.015 M^{-1}, in good agreement with the values at higher concentration of amine.

When the formation of ketimine was monitored at 280 nm (pH 10.9, [amine] = 0.402 *M*), it was found that the absorbance decreased about 7%, with a rate constant indistinguishable[14b] from the one calculated from the data at 235 nm. An absorbance decrease of 6% would be expected on the basis of $K = 0.15$ M^{-1} and [amine] = 0.4 *M*. The good agreement between the amount of diacetone alcohol lost and the amount of

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(11) W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.*, 957 (1938).

(12) For example, after taking into account the standard deviations in both the value of the rate constant at pH 12.44 and the value of k^{lim}, there is a discrepancy of about 35% between the calculated and observed values of k at this pH. This difference can be explained by assuming that addition of 0.4 *M* *n*-propylamine lowers the magnitude of the hydroxide-catalyzed rate constant by about 12%. In order to explain the discrepancy between the calculated and observed rate constants at pH 12.67, it is only necessary to assume a lowering of the hydroxide-catalyzed rate constant by 7% on addition of 0.4 *M* amine. It is not unreasonable to ascribe these discrepancies to a medium effect since a medium effect on a hydroxide ion catalyzed rate of about this order of magnitude on addition of 0.4 *M* amine may be seen for the hydrolysis of the ketimine from diacetone alcohol and *n*-propylamine, which involves[13] attack of hydroxide on the protonated ketimine (see Table II). Other evidence which indicates that the drop in rate at high pH is an artifact is the fact that there is no drop in rate at high pD in D_2O; in this case the hydroxide rate is not an appreciable fraction of the total rate even at high pD. An alternative explanation that the drop in rate at high pH may be due to a dependence (at least in part) on a term in $[\text{amine}]^2[H^+]$ is unlikely for the following reasons. (1) The plots of k^{obsd} *vs.* [amine] are linear at all pH's; there is no hint of dependence on a term in $[\text{amine}]^2$; (2) there is no corresponding drop in rate at high pD in D_2O; and (3) a term in $[\text{amine}]^2[H^+]$ *has* been observed[10] for a related reaction, and it does cause a drop in rate at high pH but the drop occurs at a lower pH and is much more severe. A change in rate-determining step to one which is dependent on the concentration of hydronium ion at pH > 12 is a formal possibility, but it is difficult to envision a mechanism which would allow this.

(13) W. P. Jencks, *Progr. Phys. Org. Chem.*, 2, 96 (1965).

(14) (a) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, 79, 5441 (1957); (b) It is difficult to monitor the reaction at this wavelength, due to the large background absorbance of diacetone alcohol, which is itself changing. A rate constant of 5.5 ± 0.8 sec^{-1} was obtained at 280 nm, which may be compared with the value of 6.7 ± 0.1 obtained at 235 nm.

ketimine formed indicates that there is no appreciable concentration of other species (*i.e.*, the carbinolamine) in solution.

The absolute values of these equilibrium constants might be slightly in error since they depend on the assumed extinction coefficient, but the values are similar to those observed for other reactions of this type. For example, the equilibrium constant for ketimine formation[6] from acetone and methylamine is 0.22 M^{-1} and for acetone and *n*-butylamine it is 0.08 M^{-1}. In any case, the isotope effect on the equilibrium is almost certainly accurate.

The observed rates of formation of the intermediate ($k_{\text{ket}}^{\text{obsd}}$) are given in Table II. There appears to be a slight medium effect, with the rates going down at high amine concentrations, but there is no dependence on the pH in the range investigated. An approximate rate constant of $7.0 \pm 0.5 \times 10^{-2}$ sec^{-1} may be calculated for the reaction in water and $5.3 \pm 0.1 \times 10^{-2}$ sec^{-1} for the reaction in deuterium oxide (leaving out the point at high amine concentration). With the assumption that the intermediate returns to reactants at a much greater rate than it goes on to products, the observed rates are given by eq 3 and the equilibrium constant by eq 4, where k_1 is the forward rate constant and k_{-1} is the back rate constant. Values for the rate constants

Table II. Formation of Ketimine from Diacetone Alcohol and *n*-Propylamine

No. of points	[Amine]	pH	k^{obsd}, sec^{-1}
2	0.0638	10.84	$7.41 \pm 0.20 \times 10^{-2}$
2	0.266	10.88	$7.37 \pm 0.04 \times 10^{-2}$
2	0.399	10.85	$6.71 \pm 0.10 \times 10^{-2}$
3	0.414	11.75	$6.49 \pm 0.08 \times 10^{-2}$
		pD	
1	0.299	11.34	5.29×10^{-2}
2	0.399	11.59	$5.39 \pm 0.01 \times 10^{-2}$
1	0.650	11.91	4.21×10^{-2}

$$k_{\text{ket}}^{\text{obsd}} = k_1[\text{amine}] + k_{-1} = k_{-1}(K[\text{amine}] + 1) \qquad (3)$$

$$K = k_1/k_{-1} \qquad (4)$$

k_1 and k_{-1} can then be simply calculated from the known values of K. Calculation gives $k_1^{\text{H}_2\text{O}} = 9.7 \pm 0.9 \times 10^{-3}$ M^{-1} sec^{-1}, $k_{-1}^{\text{H}_2\text{O}} = 6.7 \pm 0.6 \times 10^{-2}$ sec^{-1}, $k_1^{\text{D}_2\text{O}} = 5.6 \pm 0.4 \times 10^{-3}$ M^{-1} sec^{-1}, $k_{-1}^{\text{D}_2\text{O}} = 4.9 \pm 0.4 \times 10^{-2}$ sec^{-1}. Solvent isotope effects then become $k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}} = 1.7 \pm 0.3$ and $k_{-1}^{\text{H}_2\text{O}}/k_{-1}^{\text{D}_2\text{O}} = 1.4 \pm 0.2$.

The rate constant for the breakdown of the intermediate to products (k_2) over the pH range studied can be calculated from expression 5. The values of

$$k^{\text{lim}} = k_2K \qquad (5)$$

$k_2^{\text{H}_2\text{O}} = 3.30 \pm 0.40 \times 10^{-3}$ sec^{-1} and $k_2^{\text{D}_2\text{O}} = 2.41 \pm 0.34 \times 10^{-3}$ sec^{-1} give an isotope effect of 1.4 ± 0.3.

Reaction rates and equilibrium constants were also determined in aqueous ethanol solutions, but here the magnitude of k_2 becomes appreciable relative to k_{-1} and eq 6 and 7 must be used. The observed steady rate constant for the formation of acetone is still given

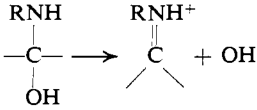
$$k_{\text{ket}}^{\text{obsd}} = k_1[\text{amine}] + k_{-1} + k_2 \qquad (6)^{15}$$

$$K = k_1/(k_{-1} + k_2) \qquad (7)$$

by eq 5. The calculated values of the various rate and equilibrium constants are given in Table III.

Discussion

Identification of the Intermediate. The identification of the rapidly formed intermediate in the reaction of *n*-propylamine and diacetone alcohol as the ketimine is reasonably secure based on the following evidence. (1) Both the rate constants and the equilibrium constants agree well with those observed for analogous reactions. For example, the rate constant for formation of the ketimine between acetone and methylamine[9] is approximately 7×10^{-2} M^{-1} sec^{-1}, which is about eight times faster than the reaction between diacetone alcohol and *n*-propylamine. This is reasonable due to greater steric hindrance in the latter case. The equilibrium constant for these two reactions is also similar, both in magnitude and in its independence on pH.[9] (2) The rate of hydrolysis of the intermediate back to starting materials (k_{-1}) is independent of pH, which is to be expected for a ketimine in this pH range. Cordes and Jencks[16] have found that the rates of hydrolysis of a series of substituted benzylidene-1,1-dimethylamines are independent of pH above pH 9, and similar findings are reported by Hine[17] for the hydrolysis of *N*-isobutylidenemethylamine. (3) The observed solvent isotope effects for this reaction are in agreement with the generally accepted mechanism for formation of ketimines from strongly basic amines and ketones,[13] involving a slow expulsion of hydroxide ion from a carbinolamine intermediate. Using the



"back of the envelope" method of Schowen,[18] an isotope effect of 1.0 may be calculated for a transition state resembling the carbinolamine and 2.0 for one resembling protonated ketimine plus hydroxide ion as limits. These values are calculated to be the same for both k_1 and k_{-1}. The observed isotope effects ($k_1^{\text{H}_2\text{O}}/k_1^{\text{D}_2\text{O}} = 1.7 \pm 0.3$, and $k_{-1}^{\text{H}_2\text{O}}/k_{-1}^{\text{D}_2\text{O}} = 1.3 \pm 0.2$) are well within these limits. The equilibrium isotope effect by Schowen's method should be 1.0 and we observe 1.34 ± 0.13.

The observation of the formation of a ketimine in this reaction does not, of course, prove that it is the active species involved. In fact, it has been suggested that the true intermediate in this reaction is the carbinolamine.[4] One of the principal reasons for this proposal was the assumption that the Schiff base could not be formed rapidly enough to account for the observed rate of reaction. This objection has now been removed by the present work. Since both the carbinol-

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(15) The approximation inherent in the derivation of this equation is that the sum of the concentrations of ketimine and diacetone alcohol is constant during the time interval of the measurement, *i.e.*, that there is no product acetone formed. It can be readily calculated that no more than 3% acetone was formed in any case during the measurement of the formation of ketimine (followed for three half-lives).

(16) E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, **85**, 2843 (1963).

(17) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

(18) R. L. Schowen, *Progr. Phys. Org. Chem.*, **9**, 275 (1972).

Table III. Effect of Solvent Composition on *n*-Propylamine Catalysis of the Dealdolization of Diacetone Alcohol

	Formation of the ketimine intermediate			
% ethanol	k_{ket}^{obsd}, sec^{-1}	k_{-1}, sec^{-1}	k_1, M^{-1} sec^{-1}	K, M^{-1}
0	$6.71 \pm 0.10 \times 10^{-2}$	$6.51 \pm 0.18 \times 10^{-2}$	$1.00 \pm 0.27 \times 10^{-2}$	0.154 ± 0.002
40	$1.29 \pm 0.02 \times 10^{-2}$	$1.12 \pm 0.04 \times 10^{-2}$	$2.93 \pm 0.04 \times 10^{-3}$	0.237 ± 0.002
60	$4.53 \pm 0.05 \times 10^{-3}$	$3.51 \pm 0.11 \times 10^{-3}$	$1.16 \pm 0.05 \times 10^{-3}$	0.269 ± 0.005
80	$1.82 \pm 0.06 \times 10^{-3}$	$1.23 \pm 0.12 \times 10^{-3}$	$6.55 \pm 0.12 \times 10^{-4}$	0.389 ± 0.004

% ethanol	No. of points	Formation of acetone[a] k, M^{-1} sec^{-1}	k_2, sec^{-1}
0	4	$5.62 \pm 0.30 \times 10^{-4}$	$3.64 \pm 0.16 \times 10^{-3}$
40	5	$2.75 \pm 0.11 \times 10^{-4}$	$1.16 \pm 0.05 \times 10^{-3}$
60	7	$2.13 \pm 0.25 \times 10^{-4}$	$7.92 \pm 0.93 \times 10^{-4}$
80	7	$1.77 \pm 0.32 \times 10^{-4}$	$4.55 \pm 0.82 \times 10^{-4}$

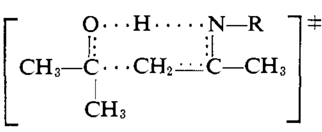
[a] The reactions were run at a total amine concentration in the range 0.2–0.4 M in 1:1 amine–amine hydrochloride buffers. The ionic strength was made up to 0.2 with KCl. The rates due to solvent catalysis in these systems were found to be small [$1.25 \pm 0.15 \times 10^{-5}$ (40% ethanol), $7.2 \pm 3.7 \times 10^{-6}$ (60% ethanol), and $8.9 \pm 4.7 \times 10^{-6}$ sec^{-1} (80% ethanol)].

amine and the ketimine are formed rapidly enough to be intermediates in the dealdolization, it is necessary to look at other criteria in order to decide which is involved. One major objection to the carbinolamine as the intermediate has been advanced by Jencks,[19] who noted that this pathway would involve a rather unlikely concerted termolecular reaction of amine on enol and enol on carbonyl compound in the reverse direction. In addition, Westheimer[6b] has shown that, in a related reaction, the ketimine from the β-keto acid 9-oxobicyclo[4.2.1]nonyl-1-carboxylic acid and aniline loses carbon dioxide at a rate 10^6 times faster than the free β-keto acid itself. This result shows clearly that ketimine intermediates of β-keto acids are labile toward decarboxylation and, by analogy, ketimine intermediates of β-hydroxy ketones should be labile toward dealdolization.

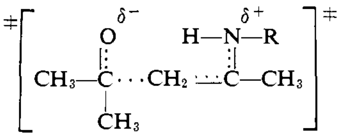
Nature of the Rate-Determining Step and the Activated Complex. The relative rates of the decomposition of the ketimine intermediate to products (k_2) and back to starting amine and diacetone alcohol (k_{-1}) show that the mechanism is best represented by a rapid preequilibrium formation of the ketimine, followed by slow decomposition to products. The ratio of k_{-1}/k_2 is about 20 in both water and D_2O. This result is in marked contrast to amine catalysis in the decarboxylation of the β-keto acid, acetoacetic acid, where the formation of the ketimine intermediate is apparently the rate-determining step.[20,20a] However, it must be pointed out that the catalyzing amine in the present case is strongly basic (pK_a = 10.9), whereas the amine used in the decarboxylation work with acetoacetic acid is the weakly basic cyanomethylamine (pK_a = 5.3).

$$\text{amine} + \text{diacetone alcohol} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{ketimine} \xrightarrow{k_2} \text{products}$$

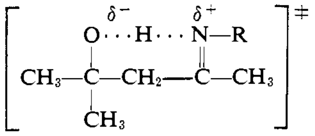
There are several possible transition states which can be envisioned for the primary amine catalyzed decomposition of diacetone alcohol. The first involves a concerted decomposition through a cyclic transition state involving both proton transfer and carbon–carbon bond cleavage (I). The second is a preequilibrium proton transfer, followed by decomposition of the zwitterion to products (II). A third possibility is that the proton transfer is a slow, rate-determining step and that the carbon–carbon bond cleavage occurs in a subsequent rapid step (III). Previously, Westheimer and Jones[21] attempted to differentiate between possibilities I and II by studying the effect of changing the dielectric constant of the medium on the rate of primary amine catalysis of dealdolization. They found that in aqueous alcohol, the observed rate is independent of the per cent alcohol up to about 75% methanol. From this they concluded that the activated complex for these reactions does not involve substantial separation of charge. These results, however, ignore the fact that in addition to changing the dielectric constant of the medium by increasing the alcohol component of the mixture, the activity of water is also being varied, and this could affect the equilibrium for the first step (formation of the ketimine). Thus, the observed effect of changing the solvent on the overall rate of dealdolization depends on both the change in polarity of the medium and the change in activity of water. Since we were able to separate the two steps of this reaction, the solvent effect was reexamined to determine the effect on the actual breakdown of the intermediate itself. This procedure allows isolation of the effect of changing the dielectric constant of the medium from the effect of changing the activity of the water. As can be readily seen from Table III, there is a change in the equilibrium constant for the formation of the ketimine and it is in the direc-



I



II



III

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[19] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 122.

[20] J. P. Guthrie and F. H. Westheimer, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **26**, 562 (1967).

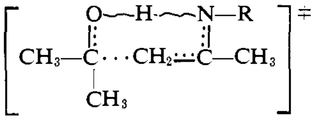
[20a] NOTE ADDED IN PROOF. It has recently been shown that neither the rate of formation of the Schiff base nor its decomposition is entirely rate determining in the cyanomethylamine-catalyzed decarboxylation of acetoacetic acid: M. H. O'Leary and R. L. Baughn, *J. Amer. Chem. Soc.*, **94**, 626 (1972).

[21] F. H. Westheimer and W. A. Jones, *ibid.*, **63**, 3283 (1941).

tion expected. As the per cent water in the medium is decreased, the amount of ketimine in equilibrium with the starting amine and ketone increases.

The rate of breakdown of the intermediate to products (k_2) shows only a modest variation with solvent composition, changing by a factor of 8 on going from water to 80% ethanol, affirming the view of Westheimer and Jones that there is very little charge separation in the transition state. As a model for what is to be expected for a completely ionic transition state, we can consider the effect of changing solvent composition on the equilibrium constant between zwitterion and uncharged forms of amino acids.[22] The effect of going from water to 90% ethanol is to favor the uncharged form by a factor of about 250 to 1400 times. A similar calculation, using the effect[23] of going from water to 80% ethanol on the pK_a's of acetic acid and ethylamine, indicates that the ion pair formed from these two compounds is favored over the neutral species in water over 80% ethanol by a factor of about 800. Thus, it appears certain that the transition state in the amine-catalyzed dealdolization does not involve a substantial separation of charge, although a slight amount would be consistent with the experimental results. This result would appear to rule out both transition states II and III, with the exception of a structure for II which is extremely product like or a structure for III which is extremely reactant like.

The low value of the observed solvent isotope effect ($k_2^{H_2O}/k_2^{D_2O} = 1.4$) indicates that no proton is undergoing translation in the rate-determining step,[24] ruling out transition state I. This situation has been treated in some detail by Swain and Schowen.[18,26] They suggest that a proton being transferred from an oxygen to a nitrogen should lie in an entirely stable potential at the transition state. Application of this concept to the present case predicts that the transition state should involve a proton in a stable potential well between the oxygen and nitrogen, while the carbon–carbon bond is undergoing cleavage. The transition state for decomposition of the intermediate according to this line of argument would look like IV with the wavy lines representing a potential well and dotted lines translation.



IV

Comparison with the Hydroxide-Catalyzed Reaction. Since the rate of breakdown of the ketimine intermediate is independent of pH over the range studied, a comparison with the rate of the hydroxide-catalyzed reaction must take into account the effect of pH. Since ketimines are moderately strong bases (p$K_a \sim 7$)[17] these molecules will exist largely as their conjugate bases below pH 7, and the rate of breakdown will *appear* to be hydroxide ion catalyzed in this pH range. Thus, a comparison can be made of the rate of the hydroxide-catalyzed dealdolization with the rate of the hydroxide-catalyzed rate of cleavage of protonated ketimine. A calculated rate constant for the reaction of hydroxide ion with the protonated form of the ketimine of diacetone alcohol and *n*-propylamine is 6.7×10^4 M^{-1} sec^{-1}. This rate constant is about 10^7 times faster than the reaction of hydroxide with diacetone alcohol itself (7.4×10^{-3} M^{-1} sec^{-1}).[4]

It is difficult to compare the magnitude of the *n*-propylamine catalysis in the dealdolization of diacetone alcohol to the aldolase system since the hydroxide-catalyzed rate for the dealdolization of fructose diphosphate is not known, but it is apparent from the present work that an intermediate ketimine can account for a rate increase of *ca.* 10^7 at pH 7. The turnover number for aldolase,[27] however, is about 30 sec^{-1}, which is about 10^5 times faster than the rate constant for the breakdown of the intermediate from *n*-propylamine and diacetone alcohol, and leads one to believe that there may be other factors involved in the enzymic catalysis other than the formation of a ketimine.

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(22) J. T. Edsall and M. H. Blanchard, *J. Amer. Chem. Soc.*, **55**, 2337 (1933).

(23) B. Gutbezahl and E. Grunwald, *ibid.*, **75**, 559 (1953).

(24) Model calculations of hydrogen isotope effects for nonlinear transition states have been performed by More O'Ferrall[25] who found that in the case where the bond angle between the reacting atoms is small the isotope effect is also small, but for cases where the transfer is part of a large ring (six atoms or greater), the isotope effect should be similar to that observed in linear system.

(25) R. A. More O'Ferrall, *J. Chem. Soc. B*, 785 (1970).

(26) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965).

(27) I. A. Rose and S. V. Rieder, *J. Biol. Chem.*, **231**, 315 (1958).