

Role of the Acidity of the Ketone in Determining the Mechanism of Enolization via Proton Abstraction from Ketone, Carbinolamine, or Imine. Catalysis of the Enolization of 2,4-Pentanedione and 3-Methyl-2,4-pentanedione by Oxyanions and by Primary, Secondary, and Tertiary Amines

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Abstract: Interconversion of the keto and enol tautomers of 2,4-pentanedione and of 3-methyl-2,4-pentanedione was studied in the presence of primary amines, secondary amines, tertiary amines, and oxyanion catalysts. All four classes of bases were found to catalyze keto-enol interconversion by the base-catalyzed proton-abstraction mechanism. This is unlike what was found for keto-enol interconversion of oxaloacetate where only oxyanions were found to follow the base-catalyzed proton-abstraction mechanism; primary, secondary, and tertiary amines followed the nucleophilic addition-elimination mechanism which involves a carbinolamine intermediate. The rate of primary and secondary amine catalyzed enolization of 2,4-pentanedione and 3-methyl-2,4-pentanedione is 10^3 - to 10^4 -fold faster than the rate of imine or enamine formation with these ketones, indicating that C-H bond labilization of the ketones is a very facile process and occurs much faster than imine formation. It is suggested that acidic ketones enolize via the base-catalyzed α -proton abstraction mechanism since removal of a proton is a more facile process than attack on the carbonyl carbon; ketones of medium acidity and non-acidic ketones enolize via the nucleophilic addition-elimination mechanism since nucleophilic attack on the carbonyl carbon is more facile than α -proton abstraction; for ketones of medium acidity, enolization via the carbinolamine intermediate is faster than imine formation while the reverse is true for non-acidic ketones. Imines, therefore, are useful intermediates for α -carbon bond labilization only in the case of non-acidic ketones.

In studies of the reaction of primary, secondary, and tertiary amines with oxaloacetic acid, we have found that all three classes of amines catalyze the interconversion of the keto and enol tautomers via a mechanism involving nucleophilic attack of amine on the carbonyl group followed by a base-catalyzed elimination reaction (eq 1).^{1,2} When primary amines are used, keto-enol interconversion is followed by imine formation, which is followed by a very slow decarboxylation. With secondary amines, keto-enol interconversion is followed by enamine formation with subsequent decarboxylation occurring through the imminium ion. When tertiary amines are employed, the only reaction observed subsequent to keto-enol interconversion is a very slow reaction attributable to the decarboxylation of oxaloacetate.

The above studies represent the first report of the enolization of a ketone via a carbinolamine intermediate rather than via the well-established base-catalyzed proton-abstraction mechanism (eq 2) that is followed when oxyanions are employed as catalysts for interconversion of the keto and enol tautomers of oxaloacetic acid. We have now undertaken a study of the reaction of 2,4-pentanedione and 3-methyl-2,4-pentanedione with primary, secondary, and tertiary amines to determine if the mechanism involving a carbinolamine intermediate is a general mechanism for all amine-catalyzed keto-enol interconversions or if some ketones enolize via the carbinolamine mechanism of eq 1 and others via the proton-abstraction mechanism of eq 2.

Experimental Section

Materials. 2,4-Pentanedione and 3-methyl-2,4-pentanedione (Aldrich) were used without further purification. Anal. Calcd for $C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 60.07; H, 8.20. Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.32; H, 8.87. All buffers were the best available commercial grades. Solids were dried in a vacuum desiccator over P_2O_5 .

Buffer Solutions. The amine buffer solutions were prepared immediately prior to use by the addition of standardized KOH or HCl to the amine hydrochloride or free amine. Phosphate buffer solutions were prepared with KH_2PO_4/K_2HPO_4 , carbonate buffers with $KHCO_3/K_2CO_3$, and acetate and formate buffers with CH_3COONa or HCO_2Na and HCl. All base catalysts were used at a pH within ± 1.0 of their pK_a allowing them to act as their own buffers. Buffer solutions were maintained at $\mu = 0.5$ (KCl) and contained 10^{-4} M EDTA. The pK_a 's of the

buffers employed were determined from pH measurements of partially neutralized solutions at 30.0 °C and $\mu = 0.5$. A minimum of five serially diluted buffer solutions were employed at each pH; the pH's of the serial dilutions agreed within ± 0.02 pH unit. Readings of pH were determined on a Radiometer Type 26 pH meter.

Kinetic Measurements. All kinetic determinations were carried out in doubly glass-distilled water containing 10^{-4} M EDTA to sequester any extraneous metal ions, with $\mu = 0.5$ (KCl). When buffer solutions were employed, the reactions were carried out under the pseudo-first-order conditions of [buffer] \gg [ketone]. Stock solutions of the ketones were allowed to equilibrate at a pH below the pK_a of the ketone or at a pH above that of the ketone pK_a . Thus upon addition of the stock solution to the kinetic solution, keto-enol interconversion could be monitored either in the overall direction of enolization or in the overall direction of ketonization. The concentration of the stock solutions was such that when added to the kinetic solution the ketone concentration was about 1.5×10^{-4} M. Each kinetic experiment was carried out with a freshly prepared solution of ketone. Rate constants were determined at 30.0 \pm 0.2 °C.

The rates of keto-enol interconversion for 3-methyl-2,4-pentanedione shown in the pH-rate profile of Figure 2b below pH 9.5 were obtained with a Radiometer pH-stat assembly specifically designed for a Cary 15 spectrophotometer.³ All other enolization rate constants, including those determined in the presence of oxyanion buffers and amine buffers, were determined with a Durrum D-150 or D-110 stopped-flow spectrophotometer equipped with a Biomation Model 805 waveform recorder. Enolization rate constants were determined by following the change in absorbance at 290 nm for 2,4-pentanedione and at 305 nm for 3-methyl-2,4-pentanedione. Rate constants for imine and enamine formation were determined on a Perkin-Elmer Lambda 3 spectrophotometer: for 2,4-pentanedione rates were determined by following the change in absorbance at 290 or 310 nm; for 3-methyl-2,4-pentanedione the change in absorbance was monitored at 330 nm.

Rate constants were calculated by manual digitation of rate traces with a Hewlett-Packard 9820A computer/9864A digitizer. Calculation of slopes and intercepts was done with the HP computer.

Results

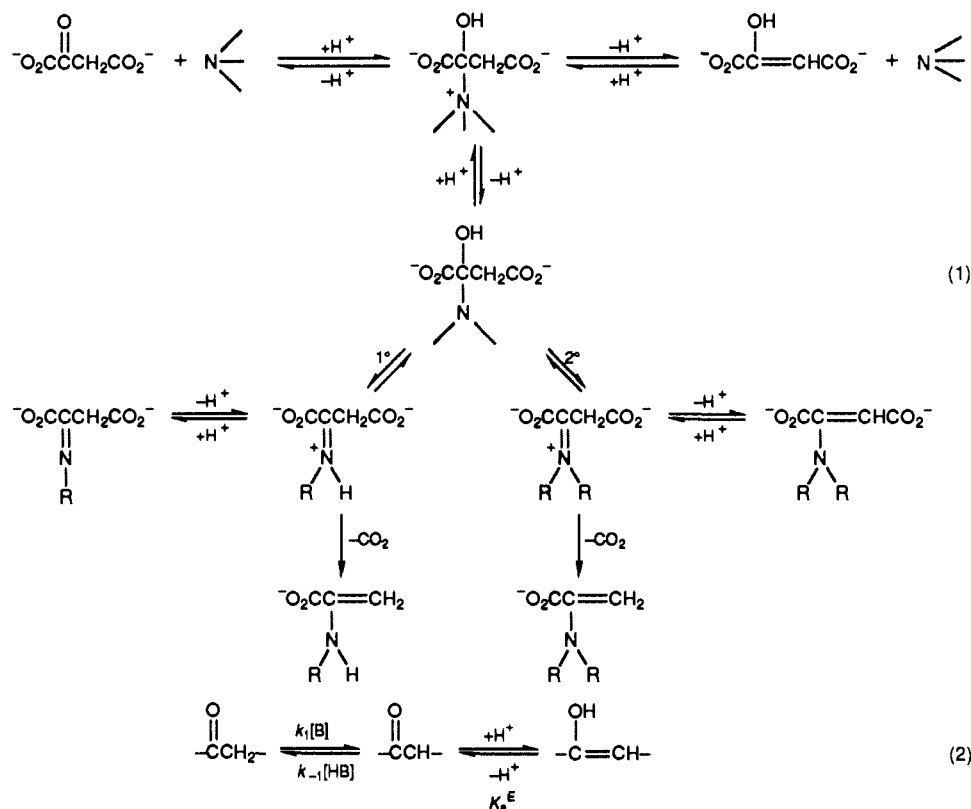
Ketone Titrations. Plots of the equilibrium absorbance of 2,4-pentanedione (at 275 nm) and 3-methyl-2,4-pentanedione (at 305 nm) as a function of pH in the absence and presence of tertiary amine are shown in Figure 1. These titration curves give values

(1) Bruice, P. Y. *J. Am. Chem. Soc.* 1983, 105, 4982.

(2) Bruice, P. Y. *J. Am. Chem. Soc.* 1989, 111, 962.

(3) Maley, J. R.; Bruice, T. C. *Anal. Biochem.* 1970, 34, 275.

Scheme 1



of 8.87 and 10.65 for the pK_a 's of 2,4-pentanedione and 3-methyl-2,4-pentanedione, respectively. These are in agreement with the previously reported values of 8.84 and 8.82 for 2,4-pentanedione⁴ and 10.8 for 3-methyl-2,4-pentanedione.⁵

Keto-Enol Interconversion. The pH-rate profile for catalysis of keto-enol interconversion by lyate species is shown in Figure 2a for 2,4-pentanedione and in Figure 2b for 3-methyl-2,4-pentanedione. The observed rate constants (open circles) were determined (a) by mixing a ketone solution equilibrated at a pH below the pK_a of the ketone with a more basic solution and monitoring the increase in absorbance occurring as the keto-enol equilibrium is shifted toward enol as a result of the sudden increase in pH (hereafter referred to as a pH increase experiment) and (b) by mixing a ketone solution equilibrated at a pH greater than that of its pK_a with a more acidic solution and monitoring the decrease in absorbance due to overall ketone formation occurring as a result of the sudden decrease in pH (hereafter referred to as a pH decrease experiment). The lines drawn through the experimental points were computer generated from the following empirical equation

$$k_{\text{obsd}} = k_a + k_b K_a / (K_a + a_H) + k_{\text{HO}^-} K_w / a_H \quad (3)$$

for 2,4-pentanedione, $k_a = 1.38 \times 10^{-1} \text{ s}^{-1}$, $k_b = 9.17 \times 10^{-1} \text{ s}^{-1}$, $pK_a = 8.27$, and $k_{\text{HO}^-} = 3.27 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$; for 3-methyl-2,4-pentanedione, $k_a = 3.68 \times 10^{-3} \text{ s}^{-1}$, $k_b = 2.36 \times 10^{-1} \text{ s}^{-1}$, $pK_a = 9.43$, and $k_{\text{HO}^-} = 3.01 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$; $pK_w = 13.83$ and a_H is the hydrogen ion activity determined at the glass electrode.

The rates of keto-enol interconversion of 2,4-pentanedione and 3-methyl-2,4-pentanedione were determined in the presence of oxyanion catalysts and in the presence of primary, secondary, and tertiary amines. All of the observed rate constants were in the stopped-flow time range. Buffer dilution plots (plots of k_{obsd} vs $[B]_T$ where $[B]_T = [\text{HB}] + [B]$ = the total concentration of catalyst present) are linear, indicating a first-order dependence of rate on catalyst concentration (Figures 3 and 4). For the

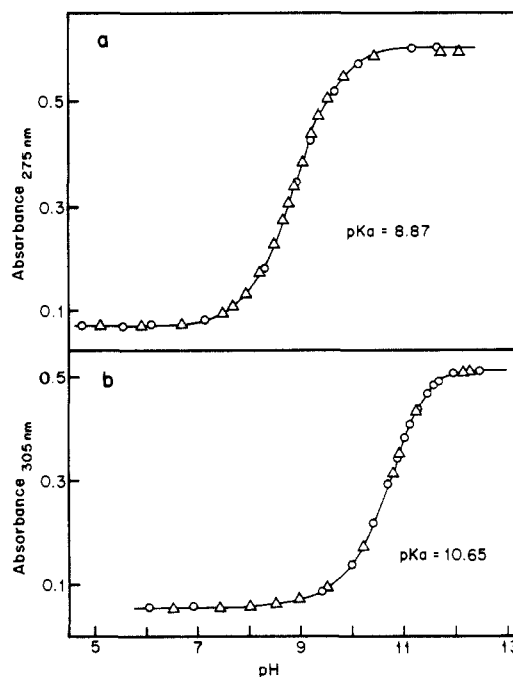


Figure 1. Equilibrium absorbance of (a) 2,4-pentanedione ($2.51 \times 10^{-5} \text{ M}$, $\mu = 0.5$ (KCl), 30°C) and (b) 3-methyl-2,4-pentanedione ($4.20 \times 10^{-5} \text{ M}$, $\mu = 0.5$ (KCl), 30°C) as a function of pH in (O) 0.5 M KCl and (Δ) 0.1 M 3-quinuclidinol minus the absorbance of 0.1 M 3-quinuclidinol.

reaction of 2,4-pentanedione or 3-methyl-2,4-pentanedione with a given catalyst, the observed rate constants obtained from pH increase experiments are identical with those obtained from pH decrease experiments (Figures 5 and 6). Plots of k_{obsd} vs $[B]_T$ maintain their linearity at very low concentrations of amine (Figure 6); constant pH at low amine concentration was maintained by carbonate buffer.

When the slopes of plots of k_{obsd} vs $[B]_T$ are divided by the mole fraction of catalyst present in the basic form ($K_a^{\text{BH}} / (K_a^{\text{BH}} + a_H)$),

(4) (a) Caldin, E. F.; Kasparian, M.; Tomalin, G. *Trans. Faraday Soc.* **1968**, *64*, 2802. (b) Crampton, M. R. *J. Chem. Soc. B* **1967**, 85.

(5) Jones, J. R. *The Ionization of Carbon Acids*; Academic Press: London, 1973; p 29.

(6) Bruice, P. Y. Unpublished data.

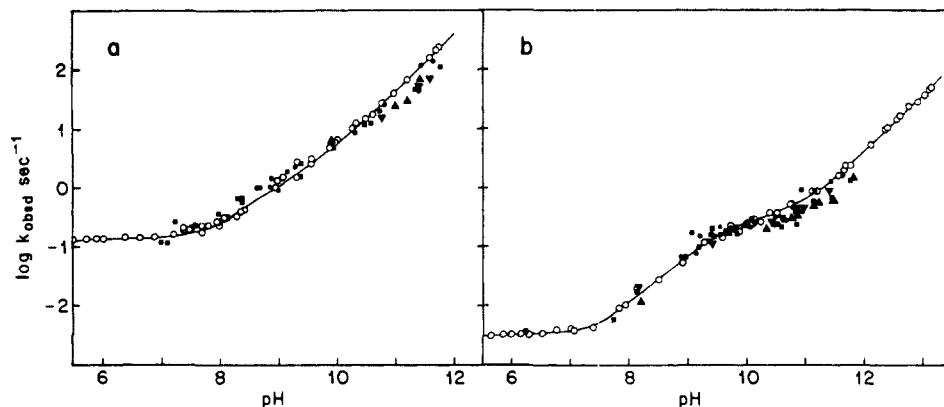


Figure 2. (a) pH-rate profile for keto-enol interconversion of 2,4-pentanedione; (b) pH-rate profile for keto-enol interconversion of 3-methyl-2,4-pentanedione. Rates were determined in the presence of lyate species (O) and from intercepts of buffer dilution plots extrapolated to zero buffer concentration employing oxygen bases (●), primary amines (▼), secondary amines (▲), and tertiary amines (■).

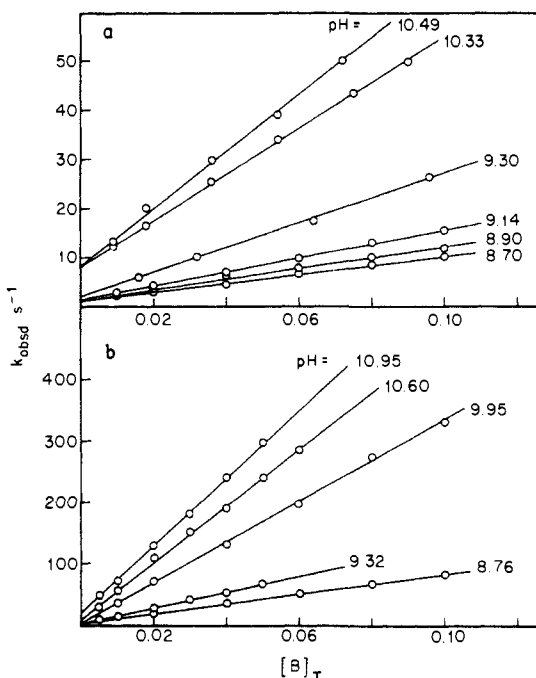


Figure 3. Plots of the observed first-order rate constants for the enolization of 2,4-pentanedione (a) in the presence of $\text{HCO}_3^-/\text{CO}_3^{2-}$ vs the total concentration of carbonate buffer at six values of pH and (b) in the presence of 3-quinuclidinol vs the total concentration of 3-quinuclidinol buffer at five values of pH.

the results obtained fall into four categories. For a given ketone, these categories depend only on the acid dissociation constant of the catalyst and are independent of whether the catalyst is an oxyanion or a primary, secondary, or tertiary amine. These results are accounted for by the rate expression of eq 4, where k_{ly} is the

$$k_{\text{obsd}} = k_{ly} + k_{gb} \frac{K_a^{\text{BH}}}{K_a^{\text{BH}} + a_H} [\text{B}]_T + k_{ga} \frac{K_a^{\text{E}}}{K_a^{\text{E}} + a_H} \frac{a_H}{K_a^{\text{BH}} + a_H} [\text{B}]_T \quad (4)$$

rate of the lyate species catalyzed reaction, k_{gb} and k_{ga} are the second-order rate constants for general base and general acid catalysis, K_a^{BH} is the acid dissociation constant of the catalyst, and K_a^{E} is the acid dissociation constant of enol. In the case of the most basic catalysts, only general base catalysis is observed. For somewhat less basic catalysts, both general base and general acid catalysis are significant and $a_H \ll K_a^{\text{E}}$. With even less basic catalysts, plots of $\text{slope}/K_a^{\text{BH}}/(K_a^{\text{BH}} + a_H)$ vs a_H/K_a^{BH} (eq 5) exhibit an increasing slope when $a_H < K_a^{\text{E}}$ and level off to a pH independent slope when $a_H > K_a^{\text{E}}$ (Figure 8, a and b). In the

$$\text{slope}/K_a/(K_a + a_H) = k_{gb} + k_{ga} \frac{K_a^{\text{E}}}{K_a^{\text{E}} + a_H} \frac{a_H}{K_a^{\text{BH}}} \quad (5)$$

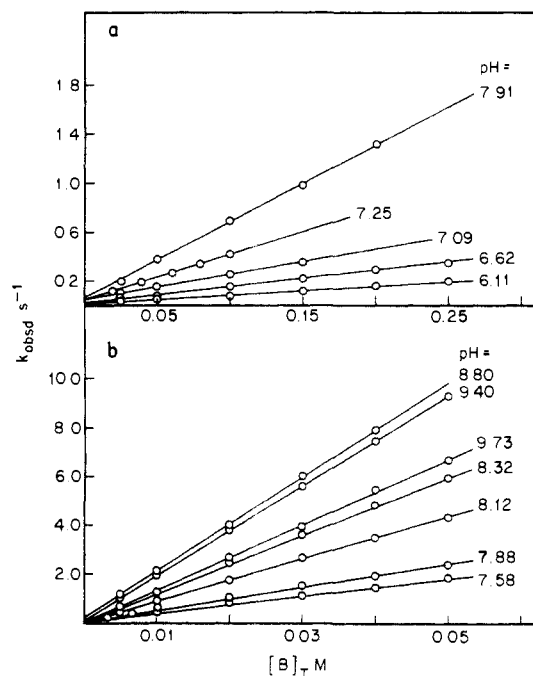


Figure 4. Plots of the observed first-order rate constants for the enolization of 3-methyl-2,4-pentanedione (a) in the presence of imidazole buffer vs the total concentration of imidazole buffer at five values of pH and (b) in the presence of 3-chloroquinuclidine vs the total concentration of 3-chloroquinuclidine buffer at seven values of pH.

case of the weakest of the base catalysts employed, $a_H \gg K_a^{\text{E}}$ and $K_a^{\text{BH}} \gg K_a^{\text{E}}$. Thus, $\text{slope}/K_a^{\text{BH}}/(K_a^{\text{BH}} + a_H)$ is equal to k_{gb} . The value of k_{gb} for each of the bases employed is given in Table I.

The acid dissociation constants (K_a^{E}) of the enol tautomers of 2,4-pentanedione and 3-methyl-2,4-pentanedione can be determined from Figure 8, a and b, respectively; rearrangement of eq 5 leads to eq 6 where F is the pH independent value of $\text{slope}/K_a^{\text{BH}}/(K_a^{\text{BH}} + a_H)$, i.e., the value of $\text{slope}/K_a^{\text{BH}}/(K_a^{\text{BH}} + a_H)$ when

$$K_a^{\text{E}} = (F - k_{gb}) \frac{K_a^{\text{BH}}}{k_{ga}} \quad (6)$$

$a_H \gg K_a^{\text{E}}$. The value of F can be obtained directly from Figure 8, a and b, and the values of k_{gb} and k_{ga} can be obtained from the intercepts and slopes, respectively, of the initial portion of the plots in Figure 8. This leads to $\text{p}K_a^{\text{E}}$ values of 8.35 for the enol tautomer of 2,4-pentanedione and 9.49 for the enol tautomer of 3-methyl-2,4-pentanedione.

The logs of the second-order rate constants for general base catalyzed enolization of 2,4-pentanedione are plotted in Figure 9 vs the $\text{p}K_a^{\text{BH}}$ of the conjugate acid of the catalyst. Oxyanion bases fall on a line that gives rise to a Bronsted β of 0.28 (cor-

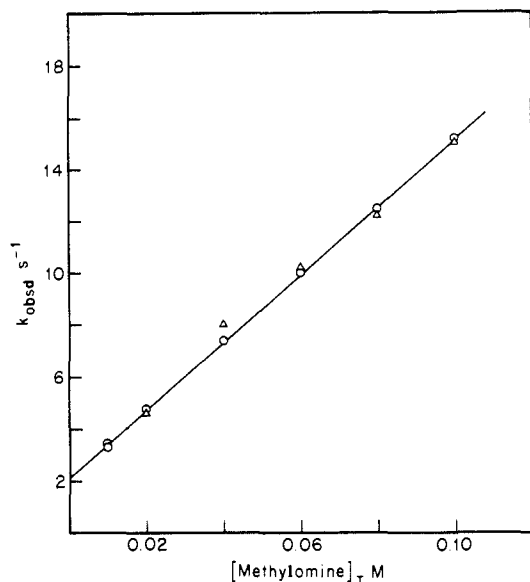


Figure 5. Observed first-order rate constants for the methylamine catalyzed enolization of 2,4-pentanedione vs the total concentration of methylamine buffer: (O) rate constants obtained upon mixing 2,4-pentanedione equilibrated at pH 6.0 with methylamine buffer at pH 9.93; (Δ) rate constants obtained upon mixing 2,4-pentanedione equilibrated at pH 10.6 with methylamine buffer at pH 9.93.

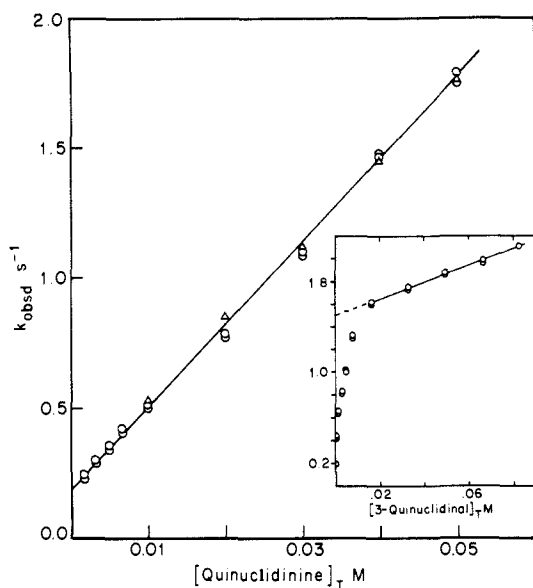


Figure 6. Observed first-order rate constants for the reaction of 3-methyl-2,4-pentanedione with quinuclidine at pH 9.91 vs the total concentration of quinuclidine. All amine solutions <0.01 M in amine contain carbonate buffer at pH 9.91: (O) rate constants obtained upon mixing 3-methyl-2,4-pentanedione equilibrated at pH 6.0 with the buffer solution; (Δ) rate constants obtained upon mixing 3-methyl-2,4-pentanedione equilibrated at pH 10.6 with the buffer solution. Inset: observed first-order rate constants for the reaction of oxaloacetic acid with 3-quinuclidinol at pH 10.00 vs the total concentration of 3-quinuclidinol. All amine solutions <0.05 M in amine contain 0.2 M carbonate buffer at pH 10.00.

relation coefficient = 0.9973); HCO_3^- and HPO_4^{2-} evidence positive deviations. Tertiary amines are more reactive than oxanions and give a Bronsted plot of similar slope ($\beta = 0.29$, correlation coefficient = 0.9917); triethylamine evidences significant steric hindrance, and imidazole falls close to the line defined by the oxanions. Primary amines fall on the line defined by oxanions. Secondary amines fall between the lines defined by tertiary amines and primary amines. Because of the steric hindrance associated with 3-methyl-2,4-pentanedione, the second-order general base catalyzed rate constants did not give meaningful Bronsted correlations. However, the same trends

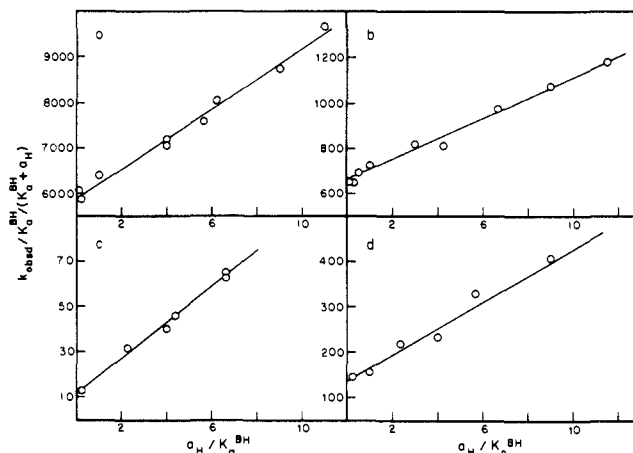


Figure 7. Plots of the slopes of buffer dilution plots divided by the mole fraction of buffer present in the basic form vs the mole fraction of buffer present in the acidic form divided by the mole fraction of buffer present in the basic form: (a) reaction of 2,4-pentanedione with 3-quinuclidinol and (b) with $\text{HCO}_3^-/\text{CO}_3^{2-}$; (c) reaction of 3-methyl-2,4-pentanedione with methylamine and (d) with quinuclidine.

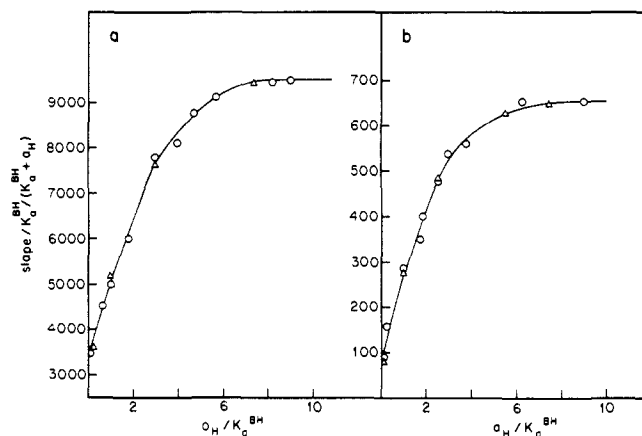


Figure 8. Plots of the slopes of buffer dilution plots divided by the mole fraction of buffer present in the basic form vs the mole fraction of buffer present in the acidic form divided by the mole fraction of buffer present in the basic form; (O) rate constants for the buffer dilution plots were obtained by mixing the ketone equilibrated at pH 6.0 with the more basic buffer solution; (Δ) rate constants for the buffer dilution plots were obtained by mixing ketone equilibrated at a pH greater than the pH of the buffer solution: (a) reaction of 2,4-pentanedione with 3-chloroquinuclidine; (b) reaction of 3-methyl-2,4-pentanedione with 3-quinuclidinol.

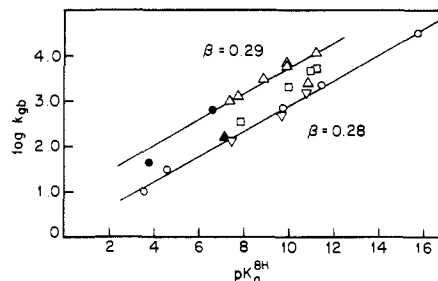


Figure 9. Bronsted plots for the general base catalyzed enolization of 2,4-pentanedione employing oxanions (O), HCO_3^- and HPO_4^{2-} (●), tertiary amines (Δ), imidazole (\blacktriangle), secondary amines (\square), and primary amines (∇) as catalysts.

observed with the unsubstituted ketone were evident with the methyl-substituted ketone: tertiary amines are more reactive than secondary amines which are more reactive than primary amines and oxanions, imidazole is considerably less reactive than a saturated tertiary amine of the same pK_a , and HCO_3^- and HPO_4^{2-} exhibit positive deviations.

Table I. Second-Order Rate Constants for Base-Catalyzed Keto-Enol Interconversion of 2,4-Pentanedione and 3-Methyl-2,4-pentanedione

	pK_a^{BH}	$k_{gb}, M^{-1} s^{-1}$	
		2,4-pentanedione	3-methyl-2,4-pentanedione
oxygen bases			
hydroxide	15.75	3.27×10^4	301
PO_4^{3-}	11.48	2260	17.4
carbonate	9.76	680	5.80
HPO_4^{2-}	6.60	630	9.50
acetate	4.56	31.2	5.97×10^{-1}
bicarbonate	3.76	43.4	7.40
formate	3.52	10.1	2.60×10^{-1}
water	-1.74	2.49×10^{-3}	6.63×10^{-5}
tertiary amines			
quinuclidine	11.20	11500	125
triethylamine	10.86	2450	3.90
trimethylamine	9.94	6950	85.0
3-quinuclidinol	9.91	6060	72.0
3-chloroquinuclidine	8.85	3150	111
<i>N</i> -methylmorpholine	7.74	1260	27.5
3-quinuclidinone	7.39	990	83.0
imidazole	7.14	170	7.60
secondary amines			
piperidine	11.23	5050	44.3
dimethylamine	10.99	4620	40.5
<i>N</i> -methylaminoethanol	9.98	2000	39.8
1-piperazinecarboxaldehyde	7.86	330	43.2
primary amines			
methylamine	10.79	1550	11.9
ethanolamine	9.70	480	9.7
glycine ethyl ester	7.40	130	9.4

^a The pK_a^{BH} values refer to the acid dissociation constants of the conjugate acids of the species listed.

Imine and Enamine Formation. After primary amine catalyzed keto-enol interconversion has reached equilibrium, a second reaction is observed between the ketone and the primary amine. With 2,4-pentanedione this second reaction is about 10^4 -fold slower than enolization, and with 3-methyl-2,4-pentanedione it is about 10^3 -fold slower than enolization; with both ketones the reaction evidences catalysis by both amine free base and ammonium ion. In the case of 2,4-pentanedione, the reaction is characterized by decreasing absorbance at 293 nm and increasing absorbance at 315 nm (Figure 10). The rate of change in absorbance is identical at the two wavelengths (Figure 11a). In Figure 11a it is also apparent that equilibrating the ketone at pH 6 (a pH increase experiment) or at pH 11 (a pH decrease experiment) before it is added to the buffer solution has no effect on either the value of the observed rate constant or the direction of the absorbance change. Similar results are obtained with 3-methyl-2,4-pentanedione and primary amines (Figure 11b) except that decreasing absorbance occurs at 305 nm and increasing absorbance occurs at 330 nm.

When the ketones react with secondary amines, the increase in absorbance at 293 nm (2,4-pentanedione) or at 305 nm (3-methyl-2,4-pentanedione) observed in pH increase experiments and attributable to keto-enol interconversion is followed by a further increase in absorbance at the same wavelength. The rate of this second reaction is about 10^4 -fold slower with 2,4-pentanedione and 10^3 -fold slower with 3-methyl-2,4-pentanedione than is the rate of enolization. Identical with what was found with primary amines, the slow reaction is subject to catalysis by both amine free base and ammonium ion.

When 2,4-pentanedione and 3-methyl-2,4-pentanedione react with tertiary amines, no amine-catalyzed reaction is observed subsequent to enolization. What is observed is a very slow reaction whose rate is independent of amine concentration and dependent on the pH of the reaction mixture, the rate increasing with increasing concentration of hydroxide ion. The reaction is characterized by decreasing absorbance at 293 and 305 nm for 2,4-pentanedione and 3-methyl-2,4-pentanedione, respectively. The

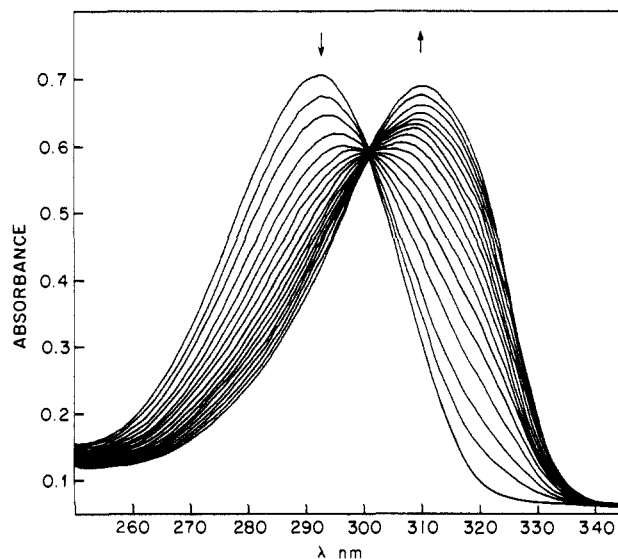


Figure 10. Repetitive scan of the reaction of 2,4-pentanedione with 0.10 M ethanolamine at pH 9.70.

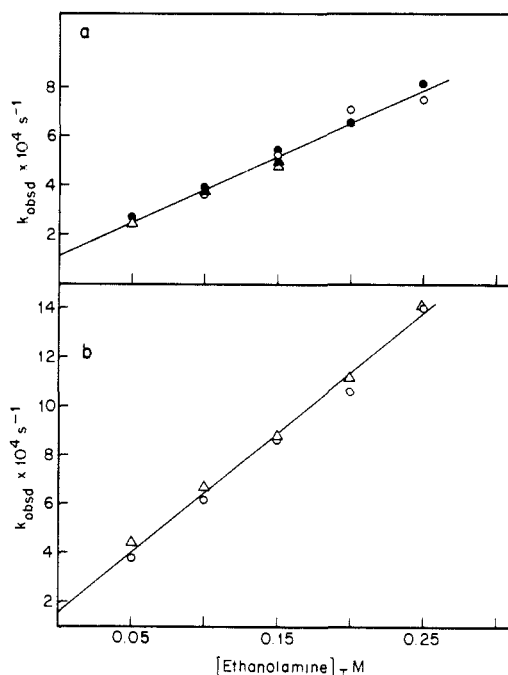


Figure 11. (a) Observed first-order rate constants for the reaction, following keto-enol interconversion, of 2,4-pentanedione with ethanolamine vs the total concentration of ethanolamine at pH 8.92: rate constants obtained by monitoring (O) the decrease in absorbance at 290 nm in pH increase experiments, (Δ) the decrease in absorbance at 290 nm in pH decrease experiments, (\bullet) the increase in absorbance at 310 nm in pH increase experiments, and (\blacktriangle) the increase in absorbance at 310 nm in pH decrease experiments. (b) Observed first-order rate constants for the reaction of 3-methyl-2,4-pentanedione with ethanolamine vs the total concentration of ethanolamine at pH 10.33: rate constants obtained by monitoring (O) the increase in absorbance at 328 nm in pH increase experiments and (Δ) the increase in absorbance at 328 nm in pH decrease experiments.

reaction also is observed in carbonate and phosphate buffer solutions, and in nonbuffered reaction mixtures. In the case of the nonbuffered reaction mixtures, the pH of the reaction solution is observed to decrease with time.

Discussion

Keto-Enol Interconversion of Oxaloacetate: Nucleophilic Addition-Elimination Mechanism. In studies of the base-catalyzed enolization of oxaloacetate we have shown that when the bases employed are oxyanions, the well-established base-catalyzed

proton-abstraction mechanism of eq 2 is followed.¹ When, however, the base is an amine, enolization takes place by the nucleophilic addition-elimination mechanism of eq 1. This is true regardless of the class of amine. Primary, secondary, and tertiary amines all follow the nucleophilic addition-elimination mechanism.^{1,2} There were three lines of evidence that demanded the postulation of a mechanism other than that of eq 2 for amine-catalyzed enolization of oxaloacetate.

1. Order in Amine. Plots of k_{obsd} vs amine concentration obtained for amine-catalyzed enolization of oxaloacetate were linear at high concentrations of amine but nonlinear at low concentrations (inset to Figure 6), indicating a first-order dependence of rate on amine concentration at high concentrations of amine and a non-first-order dependence of rate on amine concentration at low amine concentrations. The mechanism of eq 2 demands a first-order dependence of rate on amine concentration at all concentrations of amine. The mechanism of eq 1 results in a rate expression which predicts that the rate will exhibit a first-order dependence on amine concentration only at high concentrations of amine as was observed.

2. Intercepts of Buffer Dilution Plots. When the linear portions of plots of k_{obsd} vs amine concentration were extrapolated to zero amine concentration, the intercepts were found to be as much as 100-fold greater than could be attributed to lyate species catalyzed enolization at the same pH. This suggested that the extrapolated value represents the reaction of lyate species with a species other than keto or enol, i.e., reaction with a reactive intermediate.

3. Effectiveness of Amine Catalysts. Amines were found to be much more effective catalysts for the enolization of oxaloacetate than were oxyanions of the same pK_a . The relative second-order rate constants for a tertiary amine, secondary amine, primary amine, and oxyanion of $pK_a = 11$ were found to be 915:264:100:1. These values can be compared to the relative second-order rate constants of 8.1:3.1:2.3:1 that were obtained, by the same classes of bases of $pK_a = 11$, for base-catalyzed removal of a proton from nitroethane, a reaction in which amines and oxyanions are known to follow the same mechanism.⁶

Keto-Enol Interconversion of 2,4-Pentanedione and 3-Methyl-2,4-pentanedione: Base-Catalyzed Proton-Abstraction Mechanism. The results of the present study indicate that both oxyanions and amines catalyze the enolization of 2,4-pentanedione and 3-methyl-2,4-pentanedione by the base-catalyzed proton-abstraction mechanism of eq 2. Oxyanions and primary, secondary, and tertiary amines all follow this mechanism. No evidence was found for the occurrence of the nucleophilic addition-elimination mechanism.

In aqueous solution the keto and enol tautomers are in equilibrium. The equilibrium absorbance of the ketones as a function of pH are shown in Figure 1. The titration curves of Figure 1 give rise to a pK_a of 8.87 for 2,4-pentanedione and 10.65 for 3-methyl-2,4-pentanedione. The titration curves represent the conversion of the mixture of keto and enol tautomers to enolate since only the enolate anion has any significant absorbance at the wavelength of the absorbance measurement. Since the keto tautomer is the predominant tautomer in the mixture, the pK_a 's obtained from the titration curves are ketone acidity constants (pK_a^K).

From Figure 1 it is apparent that mixing a ketone solution equilibrated at a pH below its pK_a^K with a more basic solution (a pH increase experiment) will cause a shift in the keto-enol equilibrium toward enol which will be characterized by increasing absorbance with time. Mixing a ketone solution equilibrated at a pH greater than its pK_a^K with a more acidic solution (a pH decrease experiment) will shift the equilibrium toward ketone and will give rise to a rate process that will evidence decreasing absorbance with time.

At a given pH the observed rate constant (k_{obsd}) for the interconversion of keto and enol tautomers via the mechanism of eq 2 is given by the sum of the forward (k_f) and reverse (k_r) rate constants since the reaction involves an approach to an equilibrium position. This accounts for the identical rate constants that are obtained from pH increase and pH decrease experiments (Figures

5 and 6). The rate-limiting step of eq 2 may be assumed to be proton removal from carbon in the forward direction and proton donation to carbon in the reverse direction since proton donation to and from oxygen may be assumed to be rapid. Enolization was investigated at pH > 5.5, thus the B/BH pair of eq 2 is H_2O/H_3O^+ and HO^-/H_2O . The kinetic expression for the mechanism of eq 2 may be described by the rate law of eq 7 where K_a^E is the acid dissociation constant of the enol tautomer. The rate law of

$$k_{\text{obsd}} = k_f + k_r = k_1[H_2O] + k_{-1}a_H \frac{K_a^E}{K_a^E + a_H} + k_1[HO^-] + k_{-1}[H_2O] \frac{K_a^E}{K_a^E + a_H} \quad (7)$$

eq 7 is equivalent to the empirical expression of eq 3 which was used to generate the solid line pH-rate profiles of Figure 2. An acid-catalyzed term is not observed since when $a_H \gg K_a^E$, the second term of eq 7 is equal to $k_{-1}K_a^E$ and thus becomes part of the pH independent term; when $a_H \ll K_a^E$, the second term of eq 7 is equal to $k_{-1}a_H$, which is too small to be detected in the pH range of the investigation. The kinetically apparent pK_a^E values for 2,4-pentanedione and 3-methyl-2,4-pentanedione obtained from the pH-rate profiles of Figure 2 are 8.27 and 9.43, respectively. The kinetic pK_a^E values are enol acidity constants since they result from eq 7 where $K_a^E/(K_a^E + a_H)$ is the fraction of enol present as enolate.

1. Order in Amine. The plots of k_{obsd} vs $[B]_T$ obtained for the reaction of 2,4-pentanedione and 3-methyl-2,4-pentanedione with a wide variety of bases are linear (Figures 3 and 4). Unlike what was found with oxaloacetate, the linearity of the buffer dilution plots is maintained for the reaction of the ketones with amines even at very low amine concentrations (Figure 6).

2. Intercepts of Buffer Dilution Plots. The intercepts of the buffer dilution plots were obtained by extrapolation to zero buffer concentration. In the case of oxyanion bases, the intercepts fall on the pH-rate profile established for enolization (Figure 2), as was found to be the case in the oxaloacetate study. In the case of amines, the intercepts also fall on the pH-rate profile established for enolization, unlike what was found for the reaction of amines with oxaloacetate. Thus, the linearity of the buffer dilution plots and the intercepts of these plots point to the conclusion that both lyate species and amines follow the general base catalyzed mechanism of eq 2.

3. All Catalysts Obey the Same Kinetic Equation. The kinetic expression for the mechanism of eq 2 in aqueous solution in the presence of added catalysts is given in eq 8 (eq 8 is equivalent to eq 4) where $K_a^{BH}/(K_a^{BH} + a_H)$ is the mole fraction of the

$$k_{\text{obsd}} = k_y + k_1 \frac{K_a^{BH}}{K_a^{BH} + a_H} [B]_T + k_{-1} \frac{K_a^E}{K_a^E + a_H} \frac{a_H}{K_a^{BH} + a_H} [B]_T \quad (8)$$

catalyst present in the basic form, $a_H/(K_a^{BH} + a_H)$ is the mole fraction of the catalyst present in the acid form, and $K_a^E/(K_a^E + a_H)$ is the mole fraction of enol present as enolate. The k_1 and k_{-1} terms of eq 8 are equivalent to the k_{gb} and k_{ga} terms of eq 4, respectively.

The catalysts employed in this study fall into four groups. The catalysts in Group I are the most basic of the catalysts investigated; for these catalysts, $\text{slope}/K_a^{BH}/(K_a^{BH} + a_H)$ gives a constant (k_1) since $k_1 > k_{-1}$. Group II catalysts are somewhat less basic; for these catalysts, k_{-1} becomes important relative to k_1 and, since $a_H \ll K_a^E$, plots of $\text{slope}/K_a^{BH}/(K_a^{BH} + a_H)$ vs a_H/K_a^{BH} are linear (Figure 7). Group III catalysts are even less basic; for these catalysts, a_H approaches K_a^E and, therefore, plots of $\text{slope}/K_a^{BH}/(K_a^{BH} + a_H)$ vs a_H/K_a^{BH} are nonlinear. When $a_H < K_a^E$ the plots are linear, but as a_H increases and exceeds K_a^E , the plots level off and become pH independent when $a_H \gg K_a^E$ (Figure 8). For the least basic catalysts (Group IV), $\text{slope}/K_a^{BH}/(K_a^{BH} + a_H)$ is again equal to k_1 since $a_H \gg K_a^E$ and $K_a^{BH} \gg K_a^E$. All the catalysts employed in this study, amines as well as oxyanions, obey the rate equation of eq 8. Which of the four groups a particular catalyst falls into depends only on the pK_a^{BH} of the catalyst and

the pK_a^E of the enol; whether a catalyst is an amine or an oxyanion is not important. This is convincing evidence that all the catalysts employed in this study catalyze the interconversion of the keto-enol tautomers by the same mechanism, the general base catalyzed proton abstraction mechanism of eq 2.

The data in Figure 8 give a pK_a^E value of 8.35 for the enol tautomer of 2,4-pentanedione and a pK_a^E value of 9.49 for the enol tautomer of 3-methyl-2,4-pentanedione. These may be compared to the pK_a^E values of 8.27 and 9.43 obtained from the pH-rate profiles of Figure 2. The pK_a^E values of the enol tautomers are less than the pK_a^K values of the keto tautomers (8.87 for 2,4-pentanedione and 10.65 for 3-methyl-2,4-pentanedione) as expected since $pK_a^K = pK_a^E + pK_E$ where K_E is equal to $[\text{enol}]/[\text{keto}]$.

4. Effectiveness of Amine Catalysts. The second-order general base catalyzed rate constants listed in Table I describe the effectiveness of the catalysts in removing a proton from the α -carbon of the ketone. Tertiary amines are more effective catalysts than are oxyanions of the same pK_a (Figure 9). A tertiary amine of $pK_a = 11$ is 7.4 times more reactive than an oxyanion of the same pK_a . This is similar to the rate difference of 8.1 for the enhanced reactivity of a tertiary amine compared to an oxyanion of $pK_a = 11$ in removing a proton from the α -carbon of nitroethane, a reaction where both classes of catalysts are known to operate by the same mechanism. It is very different from the rate difference of 915 observed in the enolization of oxaloacetate where the two types of catalysts operate by different mechanisms.

The somewhat greater reactivity of tertiary amines compared to oxyanions in catalyzing the removal of a proton from carbon is what would be expected for a reaction involving a carbanion-like transition state. Removal of a proton by a tertiary amine leads to a transition state in which the developing negative charge on carbon is electrostatically stabilized by the developing positive charge on the nitrogen atom of the amine. When negatively charged oxygen bases are employed as catalysts, the electrostatic effects in the transition state are destabilizing. Secondary amines are less reactive than tertiary amines but are more reactive than primary amines. It may be that hydrogen bonding by the solvent to the protons on nitrogen decreases the concentration of positive charge on the nitrogen atom thereby decreasing the degree of electrostatic stabilization of the transition state. The positioning of catalysts on Bronsted plots according to charge type has been noted previously in reactions involving proton transfer.⁷

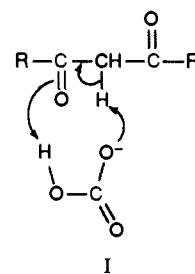
As a result of its steric properties, triethylamine shows a pronounced negative deviation from the Bronsted plot established for the reaction of tertiary amines with 2,4-pentanedione. Steric hindrance toward proton removal from carbon has been well documented.⁸⁻¹¹ Introduction of the 3-methyl substituent increases the steric parameters of the reaction to the point that it is difficult to obtain meaningful Bronsted β values for 3-methyl-2,4-pentanedione. Similar to what was observed for the unsubstituted ketone, tertiary amines were found to be more effective catalysts than secondary amines which were more effective than primary amines which were somewhat better than oxyanion catalysts.

Using temperature jump methods, Ahrens and co-workers have studied the rate of proton removal from 2,4-pentanedione by many different base types over a 16 unit pK_a range.¹² They did not

have sufficient data for any one base type to determine whether different base types fall on different Bronsted plots. They did report that data obtained over this wide a pK_a range gave rise to a curved Bronsted plot. This is in agreement with the value reported in Table I for water-catalyzed proton removal from 2,4-pentanedione. If the linearity of the Bronsted plot shown in Figure 9 were maintained, the rate constant for water-catalyzed proton removal would exhibit a negative deviation of more than 3 log units. The negative deviations frequently observed for water are significantly smaller than that, indicating that the linearity of the Bronsted plot is not maintained over a wide range of pK_a .

Imidazole Catalysis. The second-order rate constant for catalysis by imidazole falls on the Bronsted plot for primary amines rather than on that for tertiary amines. This decreased reactivity of imidazole compared to a saturated tertiary amine is most likely due to a decrease in the degree of electrostatic stabilization of the carbanion-like transition state as a result of a decrease in the concentration of positive charge on the attacking nitrogen atom by resonance delocalization to the other ring nitrogen. Imidazole and *N*-methylimidazole have been found to be less reactive than saturated tertiary amines of the same pK_a in the base-catalyzed ionization of nitroethane,^{7a} in the base-catalyzed dedeuteriation of isobutyraldehyde-2-*d*,⁸ and in the base-catalyzed elimination of hydrogen chloride from 9-fluorenylmethyl chloride.⁹ On the other hand, imidazole was found to exhibit reactivity similar to a saturated tertiary amine in the base-catalyzed elimination of acetic acid from 4-methyl-4-acetoxy-2-pentanone^{7c} and from 9-acetoxy-10-methyl-*cis*-decalone-2.¹⁰ The reactivity of imidazole (and *N*-methylimidazole) compared to the reactivity of a saturated tertiary amine in proton-transfer reactions may depend on the nature of the transition state. Proton-transfer reactions in which imidazole is found to be a less effective catalyst than a saturated tertiary amine may be those with carbanion-like transition states and thus reactivity differences are a result of differences in the degree of electrostatic stabilization of the transition state. Proton-transfer reactions in which imidazole and a saturated tertiary amine possess similar reactivities may be those with E_2 -like transition states that possess little or no formal charge.

Bifunctional Catalysis. Bicarbonate and monohydrogen phosphate evidence positive deviations from the Bronsted plot defined by oxyanions. Both of the ketones employed in this study exhibit enhanced reactivity in the presence of these catalysts. The unusual catalytic ability of these buffers is most likely due to their ability to promote a concerted cyclic proton shift (I). Of the



investigated basic catalysts, only bicarbonate and monohydrogen phosphate are bifunctional catalysts, possessing both an acidic and a basic group attached to a central carbon. Unusual catalytic effects have been observed for bifunctional catalysts in several other systems.¹³

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Choice of Mechanism. The interconversion of the keto and enol tautomers of 2,4-pentanedione and 3-methyl-2,4-pentanedione occurs via the general base catalyzed proton abstraction mechanism of eq 2 regardless of the nature of the basic catalyst employed. The interconversion of the keto and enol tautomers of oxaloacetate occurs via the mechanism of eq 2 only when the basic catalyst is an oxyanion. When primary, secondary, or tertiary amines are employed as catalysts, the interconversion of the tautomers of oxaloacetate follows the nucleophilic addition-elimination mechanism of eq 1. Whether an amine follows the general base catalyzed proton abstraction mechanism or the nucleophilic addition-elimination mechanism in catalyzing keto-enol interconversion may depend on the ease with which a proton can be removed from the ketone. The pK_a^K 's of the ketones that follow the proton abstraction mechanism in the presence of amine catalysts are 8.87 (2,4-pentanedione) and 10.65 (3-methyl-2,4-pentanedione). Oxaloacetate, which follows the nucleophilic addition-elimination mechanism with amine catalysts, has a pK_a^K of 13.04.¹ Thus one might expect those ketones with protons that are relatively easily removed to follow the proton abstraction mechanism of eq 2 in the presence of amines. In the case of ketones possessing less labile protons, attack of the amine may occur preferentially on the sp^2 -hybridized carbon atom, leading to a tetrahedral intermediate and the nucleophilic addition-elimination mechanism of eq 1.

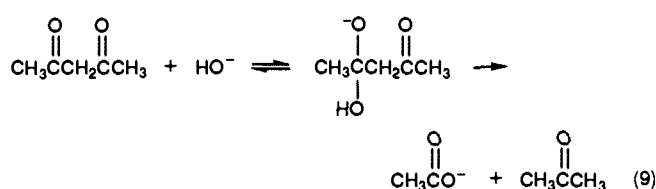
Imine and Enamine Formation. After a primary amine has catalyzed the keto-enol interconversion of 2,4-pentanedione or 3-methyl-2,4-pentanedione, it reacts with the ketone to form an imine. Imine formation is a much slower reaction than primary amine catalyzed enolization. Imine formation with 2,4-pentanedione is about 10^4 -fold slower than primary amine catalyzed enolization, and with 3-methyl-2,4-pentanedione imine formation is about 10^3 -fold slower than enolization.

In Figure 10 it can be seen that in the reaction of ethanolamine with 2,4-pentanedione, the increase in absorbance at 315 nm due to imine formation is accompanied by a decrease in absorbance at 293 nm due to loss of enolate absorbance. The rate of increase in absorbance at 315 nm is equal to the rate of loss of absorbance at 293 nm (Figure 11a). Whether the ketone is equilibrated at pH 6 or at pH 11 before being added to the reaction mixture has no effect on the direction of the absorbance change at 315 or 293 nm. That is because keto-enol interconversion, where pH increase experiments evidence increasing absorbance and pH decrease experiments evidence decreasing absorbance, has reached equilibrium on a time scale that is not detectable in Figure 10. In the investigated pH range, imine formation is observed to take place by both a general acid and a general base catalyzed pathway. Similar data were obtained for the reaction of primary amines with 3-methyl-2,4-pentanedione (Figure 11b) except that imine formation occurs at 330 nm and enolate absorbance disappears at 305 nm.

Secondary amines react with 2,4-pentanedione and with 3-methyl-2,4-pentanedione to form enamines. The time scale for enamine formation is much slower than that for secondary amine catalyzed enolization, about 10^4 -fold slower in the case of 2,4-pentanedione and about 10^3 -fold slower with the methyl-substituted ketone. Enamine formation is subject to both general acid and general base catalysis.

In the reaction of tertiary amines with the ketones, no amine catalyzed reaction is observed to occur subsequent to tertiary amine catalyzed keto-enol interconversion. This is expected since tertiary amines cannot form imines or enamines with ketones. There is, however, a very slow hydroxide ion catalyzed reaction. Buffer species have no effect on the rate of this reaction. This reaction can be attributed to hydroxide ion catalyzed cleavage of the ketone as shown in eq 9. If the reaction is carried out in nonbuffered solutions, pH of the reaction mixture decreases with time as a result of the consumption of hydroxide ion.

Conclusion. Whether amine catalyzed enolization takes place via the proton-abstraction mechanism of eq 2 or via the nucle-



philic addition-elimination mechanism of eq 1 depends on the pK_a^K of the ketone. Whether or not imine formation serves to stabilize the α C-H bond of the ketone also depends on the pK_a^K of the ketone.

A ketone has two sites for reaction with an amine, the carbonyl group and the proton on the carbon α to the carbonyl group. For relatively acidic ketones (2,4-pentanedione with a pK_a^K of 8.87 and 3-methyl-2,4-pentanedione with a pK_a^K of 10.65), proton removal is a more facile process than nucleophilic attack on the carbonyl carbon. Enolization of the ketones, therefore, will be expected to take place via the general base catalyzed α -proton abstraction mechanism of eq 2. Since proton abstraction is a more facile process than carbinolamine formation, enolization is a more rapid process than imine formation for these acidic ketones. Obviously, for such ketones, imine formation does not play a role in α C-H bond labilization.

For less acidic ketones (oxaloacetate with a pK_a^K of 13.04), nucleophilic attack on the sp^2 -hybridized carbon is more facile than removal of a hydrogen from an α -carbon atom. Enolization of the ketone, therefore, will be expected to take place via the nucleophilic addition-elimination mechanism of eq 1 rather than via the base-catalyzed α -proton abstraction mechanism of eq 2.

The nucleophilic addition-elimination mechanism involves the formation of a carbinolamine intermediate. If the amine employed is tertiary, the carbinolamine serves as an intermediate only for enolization. If the amine employed is primary or secondary, the carbinolamine serves as an intermediate for both enolization and imine formation. The relative rates of the two processes will depend on the pK_a^K of the ketone. If the pK_a^K of the α -proton of the ketone is high (e.g., acetone with a $pK_a^K = 19$), enolization will be slower than imine formation since the former involves α -proton abstraction. For such ketones, imine formation serves to stabilize the α C-H bond.¹⁴ If the pK_a^K of the "less acidic ketone" is low, the carbinolamine should lead to enolization more rapidly than it leads to imine formation.

Thus, there are three categories of ketones. Acidic ketones enolize via the α -proton abstraction mechanism; ketones of medium acidity enolize via the nucleophilic addition-elimination mechanism, and enolization is faster than imine formation; non-acidic ketones also enolize via the nucleophilic addition-elimination mechanism, and enolization is slower than imine formation. Imine formation serves to stabilize a bond on the α carbon only in the case of non-acidic ketones.

Oxaloacetate with a pK_a^K of 13.04 appears to be at the dividing line of the medium acidic and non-acidic ketones and, therefore, the relative rates of enolization and imine formation are dependent on the pK_a of the amine employed.² Elimination of ammonium ion from the carbinolamine to give ketone or enol was determined to be a general base catalyzed process; dehydration of the carbinolamine derived from primary amines to give an imine was found to be predominately a general acid catalyzed process, while dehydration of the carbinolamine derived from secondary amines was not subject to general or specific catalysis. Thus with strongly basic amines, enolization was found to be a faster rate process than imine formation. As the basicity of the amine decreased, the rate of general base catalyzed enolization decreased while the rate of general acid catalyzed dehydration increased (primary amines) or remained constant (secondary amines). Consequently with amines of $pK_a < 9$, oxaloacetate undergoes imine or enamine formation faster than it undergoes enolization.

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