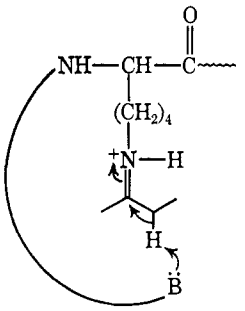
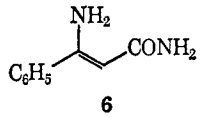


(25)

by Bender and Williams[9] based on their studies involving amine-catalyzed enolization of acetone.

It is interesting to note that there is no evidence from the present investigation to support a concerted acid–base catalysis in imine–enamine tautomerization such as that proposed for keto–enol tautomerization and investigated in the accompanying paper.[10] The absence of any base-catalyzed hydrolysis is exemplified by the fact that hydrolysis of the cyano group of **2a** to the corresponding amide, **6**, results in preference to hydrolysis of the enamine to yield the β-keto nitrile or β-keto amine.[37] Thus, whereas Banks reported concerted acid–base catalysis in the ketonization of oxaloacetic acid enol (26a)[38] there is no evidence to support such a mechanism in imine–enamine tautomerization (26b).



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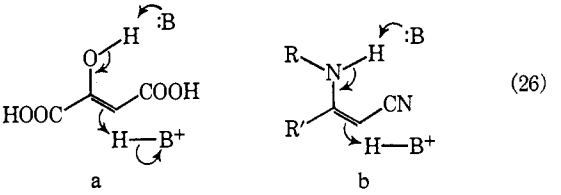

a b

(26)

Acknowledgment. This work was supported by Grant GB 5294X from the National Science Foundation and Grant AM 09171-05 from the National Institutes of Health.

(37) A. Dornow, I. Kühlcke, and F. Baxmann, *Chem. Ber.*, **82**, 254 (1949).
(38) B. E. Banks, *J. Chem. Soc.*, 63 (1962).

Intramolecular Amine-Catalyzed Ketone Enolization. A Search for Concerted Intramolecular General-Base, General-Acid Catalysis

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Abstract: A series of ketones possessing one or two tertiary amino groups has been prepared and their rate of enolization determined. Rates of enolization were determined by use of one or more of the following kinetic procedures: (a) zero-order kinetics employing ketone in excess of the iodine trapping reagents (spectrophotometric); (b) first-order kinetics employing iodine trapping reagents in great excess over ketone (pH-stat); and (c) first-order rates of racemization (polarimetric). Limitations to the application of these techniques are discussed. For those cases where more than one technique could be brought to bear on any one ketone the determined rate constants were in fair agreement. From pH–log k_{obsd} profiles for both mono- and diamines it is apparent that the mechanism of enolization is dependent upon the state of ionization of a single amino group (*i.e.*, for the diamino ketones there is no evidence for a concerted intramolecular general-acid and general-base catalyzed enolization).

A classic reaction subject to catalysis by general acids and general bases is the enolization of ketones. The possibility exists, therefore, for a concerted acid–base catalysis, indicated by the appearance of a termolecular, or product, term in the rate expression (*i.e.*, *k*[general base][general acid][ketone]). The presence or absence of this product term, and its possible significance, have been the subject of a prolonged controversy.[3] A major criticism of the termolecular mechanism has been that the magnitude of the product term is very small compared to the catalytic terms for either general-acid or general-base catalysis.[4] However, in one of the few kinetic studies involving the direct measurement of the rate of ketonization of an enol, Banks[5] reported a product term contribution of 15–23% in the case of triethanolamine or imidazole catalysis. Other workers have found smaller contributions of the product term,[6,7]

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(3) For reviews, see (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, p 334; (b) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y. 1962, p 109.
(4) K. J. Pedersen, *J. Phys. Chem.*, **38**, 590 (1934).
(5) B. E. Banks, *J. Chem. Soc.*, **63** (1962).
(6) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 124–154, and references therein.
(7) M. L. Bender and A. Williams, *J. Amer. Chem. Soc.*, **88**, 2502 (1966).

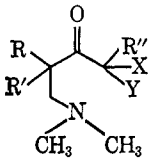
Table I. Synthetic Procedures, Physical Pryperties, and Analyses of β-Amino Ketones

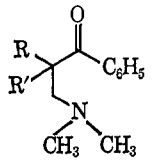
Ketone	Method	% yield	Bp (mm) or mp, °C	Lit. bp (mm) or mp, °C	n (T, °C)	Lit. n_D (T, °C)	pK_a' [a]
1a	A	20	73–75 (42)	72–74 (40)[b]	1.4242 (20)	1.4240 (20)[b]	*Ca.* 9.5
1b	B	76	37–42 (1.6–1.85)	81–83 (14)[c]	1.4336 (20.5)	1.4338 (20)[c]	9.30
1c	A	25	72–76 (13–14)	74–75 (14)[c]	1.4316 (20)	1.4311 (20)[d]	9.49
1d	C	14	79–82 (14)	82 (14)[f]	1.4398 (22)		
1e	A	48	59–64 (18.5)	60–65 (19)[e]	1.4239 (22)	1.4265 (19)[e]	*Ca.* 9.5
1f	B	75	48–51 (4)[f]		1.4305 (20)		
2a	A	62	153–156[g]	156[h]			*i*
2b	A	40	146.5–150[g]	142.5[i]			*i*
2c	D	6	110–111 (4)	95–98 (3)[k]	1.5126 (21)	1.5130 (20)[l]	*i*
3a	A	91	161–162.5 dec[g]	149[m]			
3b	A	20	174–177 dec[g,n]				
3c	C	45	148.5–150 dec[g]	156[o]			7.05
4a	B	14	197–199 dec[p]	202–203[q]			*Ca.* 9.5
4b	B	17	82–84 (3.75)[r]		1.4465 (22.5)		
4c	B	8	197–199 dec[p,s]				

[a] See text in Experimental Section. [b] A. N. Kost and V. V. Ershov, *J. Gen. Chem. USSR*, **27**, 1793 (1957). [c] R. A. Jacobsen, *J. Amer. Chem. Soc.*, **67**, 1999 (1945). [d] B. Reichert and H. Partenheimer, *Arzneim Forsch.*, **12**, 1012 (1962). [e] H. M. E. Cardwell, *J. Chem. Soc.*, 1056 (1950). [f] Monooxalate salt, mp 134–135° [*Anal.* Calcd for $C_9H_{19}NO\cdot(COOH)_2$: C, 53.42; H, 8.56; N, 5.66. Found: C, 53.40; H, 7.65; N, 5.76]; free base, mol wt 152.0 (calcd 157.2). [g] Hydrochloride salt. [h] C. Mannich and G. Heilner, *Chem. Ber.*, **55**, 356 (1922). [i] Phenyl ketones insoluble at half-neutralization at concentration of *ca.* 10^{-2} *M*. [j] E. B. Knott, *J. Chem. Soc.*, 1190 (1947). [k] N. Nazarov, E. M. Cherkasova, and C. C. Khvan, *J. Gen. Chem. USSR*, **28**, 443 (1958). [l] H. R. Snyder and J. H. Brewster, *J. Amer. Chem. Soc.*, **71**, 1061 (1949). [m] R. H. Harradance and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938); *Chem. Abstr.*, **33**, 5855 (1939). [n] A. M. Downes, N. S. Gill, and F. Lions [*J. Amer. Chem. Soc.*, **72**, 3464 (1950)] report synthesis of the free base, **5b**, and its picrate. *Anal.* Calcd for $C_{11}H_{21}NO_2\cdot HCl$: C, 56.03; H, 9.40; N, 5.94. Found: C, 56.20; H, 9.55; N, 5.92. [o] B. Reichert and H. Partenheimer, *Arch. Pharm.*, **293**, 683 (1960). [p] Dihydrochloride salt. [q] F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1376 (1959). [r] Dioxalate salt, mp 153–154.5° [*Anal.* Calcd for $C_{12}H_{26}N_2O\cdot 2(COOH)_2$: C, 48.72; H, 7.70; N, 7.10. Found: C, 49.44; H, 7.70; N, 7.52]. [s] *Anal.* Calcd for $C_{13}H_{24}N_2O_3\cdot 2HCl$: C, 47.41; H, 7.96; N, 8.50. Found: C, 47.85; H, 7.87; N, 8.63.

but in these cases conditions were maintained so as to give zero-order kinetics in the enolization reaction, using iodine as a trap for enol. The numerous problems inherent in this technique are discussed in detail below (see Discussion). The work of Banks,[5] however, lends support to the proposal that there is a small contribution

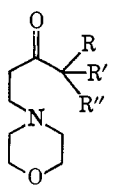
Chart I. Structures of β-Amino Ketones (Mannich Bases)

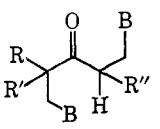




1a, R = H; R′ = H; R″ = H; X = H; Y = H
b, R = CH_3; R′ = CH_3; R″ = CH_3; X = CH_3; Y = H
c, R = H; R′ = H; R″ = CH_3; X = CH_3; Y = CH_3
d, R = H; R′ = H; R″ = H; X = CH_3; Y = C_2H_5
e, R = CH_3; R′ = H; R″ = H; X = H; Y = H
f, R = H; R′ = CH_3; R″ = H; X = CH_3; Y = CH_3
g, R = CH_3; R′ = CH_3; R″ = CH_3; X = CH_3; Y = CH_3

2a, R = H; R′ = H
b, R = H; R′ = CH_3
c, R = CH_3; R′ = CH_3



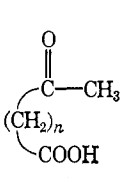


3a, R = H; R′ = H; R″ = H
b, R = CH_3; R′ = CH_3; R″ = CH_3
c, R = H; R′ = CH_3; R″ = C_2H_5

4a, R = H; R′ = H; R″ = H; B = $N(CH_3)_2$
b, R = CH_3; R′ = CH_3; R″ = CH_3; B = $N(CH_3)_2$
c, R = H; R′ = H; R″ = H; B = 

from a mechanism whose transition state is composed of the elements of ketone, a general acid, and a general base.

Since it is well known that intramolecular catalysis often is much more efficient than the corresponding intermolecular catalysis (see ref 3a, Chapter 1), substrates were designed to take advantage of this behavior in ketone enolization. A mechanism involving an intramolecular general acid and general base as the major catalytic moieties in ketone enolization would lend strong support to the "product term" discussed above for intermolecular catalysis by general acids and general bases. To test the concept of concerted catalysis of enolization, a kinetic investigation of the enolization of a series of several types of β-amino ketones (Chart I) was carried out. Intramolecular general-acid and/or general-base catalysis in enolization of ketones has been proposed by Bell and Fluendy[8] and by Harper and



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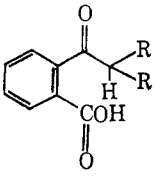

6

Bender.[9] The keto acids studied by these workers (**5**[8] and **6**[9]) are in equilibrium with the corresponding lactols in solution. This equilibrium is pH dependent in the case of **6**,[10] a fact which adds a further complication to the system.

Experimental Section

Materials. The ketones used in this research were synthesized by one of four procedures described below, and are listed in Table I

(8) R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, **59**, 1623 (1963).
(9) E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, **87**, 5625 (1965).
(10) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

together with their physical properties and analyses.[11] pK_a' values of monoamino ketones **1** and **3** were determined by half-neutralization of a 10^{-2} *M* solution at $\mu = 1.0$ with KI at 30°. The half-neutralized aryl ketones **2** were not sufficiently soluble at this concentration to determine the pK_a', although at the lower concentrations used in the kinetic measurements (*ca.* 10^{-4} *M*), lack of solubility did not appear to be a problem. Attempts to measure the two pK_a' values for diamino ketones of type **4** by the potentiometric titration method of Albert and Serjeant[12a] previously employed by Bruice and Willis[12b] for α,ω-diaminoalkanes provided only approximate p*K* values. Methyl ketones **1a** and **1e** showed an initial pH drift toward basic pH at half-neutralization. pH drifts of *ca.* 0.3 pH unit were observed over the first 2–4 hr after half-neutralization. However, no further drift in the pH of the solution was observed on standing at 30° for an additional 4 days. These changes in pH were accompanied by small changes in the ultraviolet spectra of the methyl ketones. A cursory polarographic investigation did not lend any evidence in support of a retrograde Mannich reaction[13] under the conditions employed in this research.

Procedure A. Routinely, the Mannich bases were prepared by refluxing a solution of the ketone (0.2 mol), recrystallized dimethylamine hydrochloride (0.2 mol), and paraformaldehyde (0.32 mol) in alcohol, containing a catalytic amount of 12 *N* hydrochloric acid, for a period of from 4 to 8 hr, according to the method of Mannich and Heilner.[14] After cooling the reaction solution, the product was isolated either by filtration of the precipitated hydrochloride salt, or by neutralization of the reaction solution with solid potassium hydroxide followed by ether extraction of the free base. The products were purified by recrystallization or by distillation *in vacuo*.

Procedure B. Mannich bases of several of the more sterically hindered ketones, and all of the bis-Mannich bases, were prepared by the method of Blicke and McCarty.[15] This procedure is similar to procedure A, but glacial acetic acid is substituted for ethanol as solvent, and the reaction is carried out at 90° for 3–5 hr. The acetic acid is removed *in vacuo* and the product isolated either by precipitation with a hot acetone extraction or neutralization to give the free base. Purification of the final product was accomplished by recrystallization or distillation *in vacuo*. All attempts to prepare **1g** *via* this method failed.

Procedure C. The Mannich bases of 3-methyl-2-pentanone were prepared by the method of Reichert and Partenheimer[16] in which isopropyl alcohol is substituted for ethanol in a procedure similar to A above.

Procedure D. 3-Dimethylamino-2,2-dimethylpropiophenone (**2c**) was prepared by the method of Nazarov, *et al.*,[17] whereby isobutyrophenone (0.1 mol), aqueous dimethylamine (0.4 mol), and formalin (0.4–0.6 mol) are heated at reflux for 5 hr. Neutralization of the reaction solution with hydrochloric acid was followed by treatment of the aqueous layer with sodium carbonate and ether extraction. Distillation of the crude material *in vacuo* gave the desired product.

Resolution of Optically Active Mannich Bases. *d*-Camphor-10-sulfonic acid was dissolved in a minimum amount of warm ethyl acetate and the requisite equivalents of the Mannich base (obtained in the case of **3c** by neutralization of the hydrochloride salt and extraction with ether to give the free base suitable for resolution) were added. On cooling slowly, a crystalline material separated which could be recrystallized from ethyl acetate. In the case of **2b**, the procedure of Casy and Myers[18] was followed, using (−)-dibenzoyltartaric acid as the resolving acid to precipitate the salt in acetone. The low solubility of the dibenzoyltartaric acid salt of **2b** in water precluded its use for kinetic studies in aqueous systems. The use of *d*-camphor-π-sulfonic acid as a resolving agent for **1d** and **1f** failed to give any crystalline product with several solvents.

The use of *d*-α-bromocamphor-π-sulfonic acid ammonium salt as a resolving agent for **3c** was investigated in an attempt to obtain an optically active salt with a larger rotation than the salt obtained from **3c** and *d*-camphor-10-sulfonic acid. The resolving agent was recovered unchanged, presumably due to the inability of the weakly basic morpholine to exchange with the much more basic ammonia. Therefore, the free acid[19] was prepared and stoichiometric amounts of the free acid and **3c** were mixed together in ethyl acetate and allowed to set at −20° for 2 weeks during which time an oily substance separated. The solvent was decanted off and the residue triturated with anhydrous ethyl ether, returned to the freezer, and allowed to set for several months. During this time the solvent was replenished several times *via* decantation and addition of fresh anhydrous ether, as a more crystalline material formed. This material was not completely crystalline, however, and could not be purified further. Optically active salts prepared for this investigation are listed in Table II, together with their physical properties and analyses.[11]

Table II. Physical Properties and Analyses of Resolved β-Amino Ketones

Ketone	Resolving acid[a]	% yield	Mp, °C	$[\alpha]^{30}D$[b]
1e	C	40	129.5–132[c]	+32.35
2b	D	36	113–114.5[d]	−48.6[d]
3c	C	14	145–147[e]	+12.47

[a] C = *d*-camphor-10-sulfonic acid (Aldrich); D = (−)-dibenzoyltartaric acid (K & K). [b] All rotations were obtained in aqueous solution (*c* ~10^{-2}). [c] *Anal.* Calcd for $C_7H_{15}NO \cdot C_{10}H_{16}O_4S$: C, 56.49; H, 8.64; N, 3.88. Found: C, 56.67; H, 8.69; N, 4.06. [d] Lit.[18] mp 115–116.5; $[\alpha]^{20}D$ −53 (*c* 1.0, EtOH). [e] *Anal.* Calcd for $C_{11}H_{21}NO_2 \cdot C_{10}H_{16}O_4S$: C, 58.45; H, 8.64; N, 3.24. Found: C, 58.51; H, 8.77; N, 3.39.

Kinetics. All kinetic measurements were done at 30 ± 0.1° in aqueous solutions at $\mu = 1.0$ with KI. The amino ketone hydrochlorides were dissolved in water to give stock solutions of approximately 10^{-2} *M*. In the case of the free bases, a stoichiometric amount of 0.100 *N* hydrochloride acid was added, and water added to volume, giving a 10^{-2} *M* stock solution. Potassium triiodide solutions were prepared by addition of iodine and potassium iodide to water, giving a solution of approximately 10^{-2} *M* iodine and $\mu = 1.0$ with KI. The iodination of the amino ketones was followed titrimetrically at constant pH under pseudo-first-order conditions with the ketone being the limiting reagent. Potassium triiodide solution (25 ml) was placed in the autotitrator cell and equilibrated at 30°, and the pH adjusted with additions of approximately 0.02 *N* KOH from the micrometer syringe. The amino ketone stock solution (0.25 ml) was introduced and the reaction followed by monitoring the addition of 0.02 *N* KOH necessary to maintain constant pH. No uptake of base was observed on running the following "blank" experiments at pH 9.30: (a) addition of 0.25 ml of 10^{-2} *M* ketone stock solution to 25 ml of water; (b) addition of 0.25 ml of 10^{-2} *M* ketone stock solution to 25 ml of 1 *M* KI, (c) addition of 10^{-2} *M* $Me_3N \cdot HCl$ to 25 ml of triiodide solution (10^{-2} *M* I_2, $\mu = 1.0$); and (d) employing **2c** as substrate. Pseudo-first-order rate constants were calculated from the slopes of plots of $\ln [(\text{base added})_\infty/[(\text{base added})_\infty - (\text{base added})_t]$ *vs.* *t* or by the method of Guggenheim.[20] Linear plots generally were obtained to between 1 and 2 half-lives.

Halogenation of ketones can be followed spectrophotometrically by following the decrease in triiodide absorbance (λ_{max} 351 mμ).[7,9] In the earlier work, the use of a large excess of ketone resulted in the rates zero order in iodine, and the blank reaction of triiodide with buffer was apparently substracted from the observed rates of halogenation. In the present work, rates of enolization were too fast to follow under zero-order conditions. Under the pseudo-first-order conditions employed in this research, however, the blank rate of hydrolysis of triiodide by the carbonate, phosphate, and succinate buffers is sufficiently large so as to mask any reaction of the ketone with triiodide in all of ketones studied except **1a**. In the case of ketone **1a**, buffer (3.0 ml) containing approximately 10^{-3} *M* triiodide was equilibrated at 30° in a test tube. A stock solution of *ca.* 10^{-3} *M* ketone (30 μl) was added to the buffer, a portion of the solution transferred to a quartz cell (path length = 1 mm), and the reaction followed by watching the disappearance of triiodide at

(11) Analyses performed by A. Bernhardt, Max Planck Institute, Mülheim, Germany.

(12) (a) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962, p 51; (b) T. C. Bruice and R. G. Willis, *J. Amer. Chem. Soc.*, 87, 531 (1965).

(13) (a) P. Zuman and V. Hořak, *Collect. Czech. Chem. Commun.*, 27, 187 (1961); (b) P. Čársky, P. Zuman, and V. Hořake, *ibid.*, 29, 3044 (1964).

(14) See Table I, footnote *h*.

(15) See Table I, footnote *q*.

(16) See Table I, footnote *o*.

(17) See Table I, footnote *k*.

(18) A. F. Casy and J. L. Myers, *J. Pharm. Pharmacol.*, 16, 455 (1964).

(19) F. Hein and H. Regler, *J. Prakt. Chem.*, 148, 1 (1937).

(20) E. A. Guggenheim, *Phil. Mag.*, 2, 538 (1926).

351 mμ. A blank solution of *p*-nitrophenol was utilized to keep the OD of the highly absorbant triiodide on scale. Pseudo-first-order rates were calculated from the slopes of plots of ln $OD_\infty/(OD_\infty - OD_t)$ *vs.* *t* or by the method of Guggenheim.[20] Linear plots generally were obtained through 1.5 half-lives. An additional complication was observed in the use of phosphate buffer which rendered this buffer useless in following halogenation by triiodide. A stock solution of 0.33 *M* KH_2PO_4 at $\mu = 1.0$ with KI slowly oxidized the iodide to iodine, even under a nitrogen atmosphere, forming potassium triiodide which could be detected spectrophotometrically and observed visually as a light yellow color developed.

Racemization of the optically active amino ketone **1e** was followed polarimetrically. A stock solution *ca.* 10^{-1} *M* in amino ketone (as the *d*-camphor-10-sulfonate salt) was placed in a test tube and equilibrated at 30°. Minute amounts of KOH solutions mixed of various concentrations were added, and the combined solution was mixed well and placed on the polarimeter. The decrease in rotation with time was measured and the pH of the reaction solution measured when the reaction was complete. Pseudo-first-order rate constants were calculated from the slopes of plots of ln $\alpha_\infty/(\alpha_\infty - \alpha_t)$ *vs.* *t* or by the method of Guggenheim.[20] Linear plots generally were obtained through 1–2 half-lives.

Apparatus. A Radiometer 22 pH meter equipped with a PHA 630 PA scale expander and a Type GK 2021C combined electrode was used to determine pH. The electrode was stored at the temperature of the kinetic measurements. Titrimetric rates were determined with a Radiometer TTT 1b autotitrator equipped with a PHA scale expander and a thermostated Metrohm microtitration cell as described by Bruice and Bradbury.[21] Potentiometrically determined pK_a' values were obtained by use of the same apparatus. Spectrophotometric rates were determined with a Gilford 2000 recording spectrophotometer or a Zeiss M4Q III monochromator equipped with a Gilford multiple-sample absorbance recorder. Both instruments were equipped with dual thermospacers through which water was circulated from a Precision constant-temperature circulating water bath at 30°. Polarimetric rates were determined with a Perkin-Elmer Model 141 polarimeter with a cell thermostated at 30° and connected to a Sargent Recorder, Model SR.

Results

With ketones of type **1**, **2**, and **3**, at pH's between 5.75 and 9.2, use of the zero-order iodination trapping procedure,[7-9] with the ketone in large excess over iodine, resulted in complete loss of the absorbance due to triiodide at 351 mμ by the time the reactants could be mixed and the cuvettes replaced in the spectrophotometer. In attempting to develop a spectrophotometric technique for monitoring enolization under pseudo-first-order conditions (*i.e.*, iodine in large excess over ketones), it became apparent that considerably more than one molecule of iodine was consumed per mole of ketone, even after correction for the blank buffer reaction. In order to assure pseudo-first-order conditions, the iodine must be present to a concentration at least 100 times that of the ketone. In order to have a change in optical density of at least 0.2, a change of I_3^- concentration of *ca.* 10^{-5} *M* is necessary. This requires an initial ketone concentration of *ca.* 10^{-5} *M* depending on the stoichiometry of the reaction. In order to assure pseudo-first-order conditions, the iodine must be present at a concentration at least 100 times that of the ketone; *i.e.*, $[I_3^-] \approx 10^{-3}$ *M*. By use of a solution of *p*-nitrophenol as a blank and cells of 1 mm length the reaction of β-amino ketones of type **1** and **2** with I_3^- could be monitored, but only in the case of **1a** was it possible to obtain reproducible results. It was apparent that a spectrophotometric assay of the reaction between I_3^- and ketones, employing either zero-order or pseudo-first-order conditions, would be of little general utility.

An alternative means of monitoring the enolization reaction was sought. A procedure involving displacement of the keto–enol equilibrium by strong acid or base and then following spectrophotometrically the return to equilibrium[22] was attempted. Similarly, attempts to obtain a spectrophotometric titration of the keto–enol equilibrium failed due to the instability of the substrate in base. The use of nuclear magnetic resonance[23] or near-infrared[7,24] spectroscopic methods requires the use of more highly concentrated solutions of substrate (*ca.* 0.1–0.5 *N*)[23a,c,24] than is desirable in studying an intramolecular process. Similarly, the use of a deuterated substrate also requires rather high concentration (*ca.* 0.1 *N*).[23a] In addition, the use of these techniques is complicated by the increasing importance of secondary isotope effects as the exchange reaction proceeds,[23b,c] resulting in uncertainties in k_{obsd} of ±20%.[23c] Since a proton is liberated in the reaction of iodine with the enolate, a pH-stat can be employed to follow enolization rates under the pseudo-first-order conditions without the necessity of employing buffers which consume I_3^- in a competing reaction.

That the liberation of protons measured by the pH-stat was associated with iodination of the enolized β-amino ketones was demonstrated by several blank experiments (see Experimental Section). The base-catalyzed hydrolysis of KI_3 or I_2 to liberate a proton was a serious limitation of this method of monitoring enolizations; an upper limit of pH 10 was placed on any rate measurements. Another limitation was imposed by the stability of the pH-stat; namely, if $k_{obsd} < 10^{-3}$ min^{-1}, pH drift occurred and the pH-stat was rendered inoperative. Owing to the magnitude of rates of enolization of the compounds studied in this work, $k_{obsd} < 10^{-3}$ min^{-1} usually was observed at pH of *ca.* 1.5 unit below pK_a. In the case of the dimethylamino adducts (**1**, **2**, **4a**, **4b**), these considerations lead to a useful pH range of *ca.* 8–10, whereas the morpholino adducts (**3c**, **4c**) could be followed over a pH range of *ca.* 6–10.

As in the case of the titrimetric methods, this indicated that anywhere from 2 to 5 mol of iodine was consumed per mole of ketone. β-Amino ketones containing fewer enolizable protons (**1b**, **1c**, **2b**, **4b**) were synthesized in an attempt to simplify the stoichiometry problem. Although a small decrease in base uptake was observed, a 1:1 stoichiometry was still not realized.

Attempts to monitor rates of enolization by following the rate of racemization of optically active β-amino ketones were successful only in the case of **1e**. The rate constants obtained polarimetrically agreed fairly well with those obtained by titrimetric methods. However, it was anticipated that **1e** would exhibit a polarimetric rate less than that of the titrimetric rate, due to the fact that statistically all four protons of **1e** are capable of being abstracted in a base-catalyzed step as measured in the iodination reaction on the pH-stat, whereas only one enolizable proton is present on the asymmetric carbon and subject to measurement by the polarimeter. In fact, the polarimetric rates are *ca.* twice the titrimetric rates at any given pH. It was possible to monitor the enolization reaction at considerably higher pH (up to pH 12) than was possible using the iodination technique,

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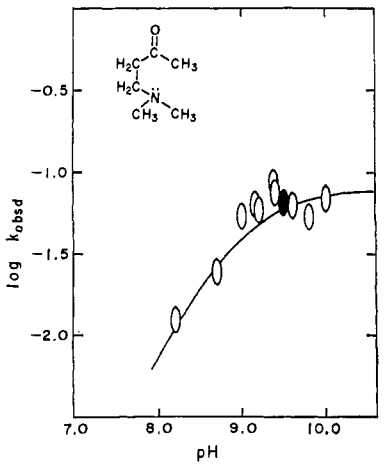


Figure 1. Titrimetrically (open ellipses) and spectrophotometrically (closed ellipse) determined pH–log k_{obsd} profiles for the enolization of 1-dimethylamino-3-butanone (**1a**). The value determined spectrophotometrically was obtained by extrapolation of a serial buffer dilution (six k_{obsd} *vs.* $[B_T]$) to $[B_T]$ = zero, using carbonate buffer at pH 9.5. The points are experimental and the curve is calculated from the rate expression 1 and the derived rate constants of Table III.

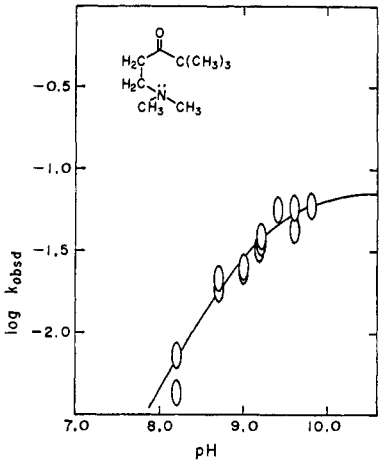


Figure 2. Titrimetrically determined pH–log k_{obsd} profile for the enolization of 1-dimethylamino-4,4-dimethyl-3-pentanone (**1c**). The points are experimental and the curve is calculated from the rate expression 1 and the derived rate constants of Table III.

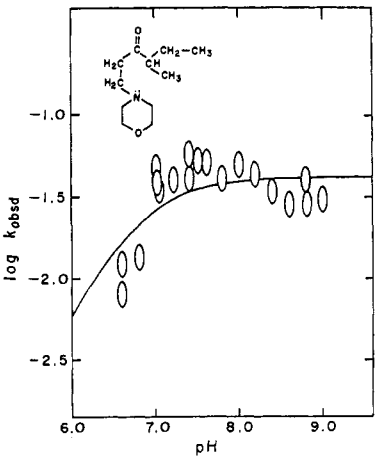


Figure 3. Titrimetrically determined pH–log k_{obsd} profile for the enolization of 1-morpholino-4-methyl-3-hexanone (**3c**). The points are experimental and the curve is calculated from the rate expression 1 and the derived rate constants of Table III.

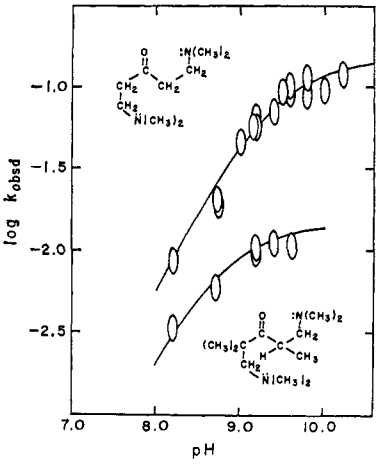


Figure 4. Titrimetrically determined pH–log k_{obsd} profile for the enolization of 1,5-bis(dimethylamino)-3-pentanone (**4a**, upper curve) and 1,5-bis(dimethylamino)-2,2,4-trimethyl-3-pentanone (**4b**, lower curve). The points are experimental and the curves are calculated from the rate expression 1 and the derived rate constants of Table III.

which gives a decided advantage to the polarimetric method. Unfortunately, the other optically active amino ketones which were resolved (Table II) could not be studied by this technique due to too small a difference between the specific rotation of the resolved amine free base (α_0) and the racemized product.

In summary, of the β-amino ketones synthesized (Chart I), the rate of enolization of only **1a** could be monitored spectrophotometrically under pseudo-first-order conditions using the iodine trapping technique, whereas **1a**, **1c**, **1e**, **3c**, and **4a** could be monitored under the same conditions of iodine trapping using the pH-stat. Of the β-amino ketones which could be resolved, the racemization of only **1e** could be monitored polarimetrically. For **1a**, good agreement was obtained between k_{obsd} determined spectrophotometrically and k_{obsd} obtained titrimetrically, and, for **1e**, fair agreement obtained between determinations of k_{obsd} by polarimetric *vs.* titrimetric methods. Thus, addition of the first iodine molecule to the enolate is the slowest of the multiple iodination steps. Iodination trapping certainly leaves much to be desired as a means for following rates of enolization. Acknowledging the experimental uncertainties in the rate data obtained, it is still possible to provide an answer to the question which this investigation set out to answer; *i.e.*, establishing the presence or absence of push–pull, or concerted general-acid, general-base catalysis as a major contributor in the enolization of β-amino ketones.

pH–log rate profiles derived from data collected within the framework of conditions imposed by the problems discussed above have the form shown in Figures 1–4 for all β-amino ketones investigated. Such a profile is indicative of a reaction catalyzed by an ionizable group, leading to a plateau rate above the pK_a of the ionizable group. This is described by eq 1. Derived

$$k_{obsd} = k_b \frac{K_a}{K_a + a_H} \qquad (1)$$

rate constants and pK_{app}'s are given in Table III. The

Table III. Constants for the Enolization of β-Amino Ketones Obtained by Following Iodination Potentiometrically at Constant pH

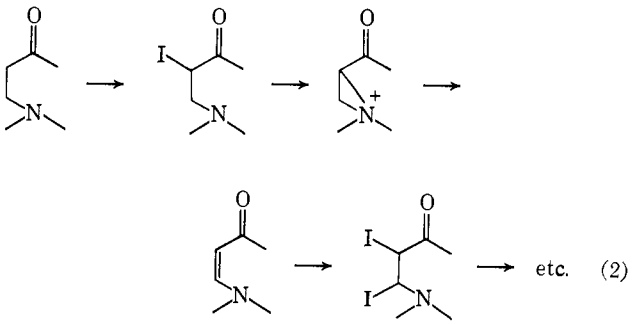
Compd	pK_{app}	$k_b \times 10^2$ min^{-1}	Mol of I_2/mol of ketone
1a	9.0	7.9	*Ca.* 4–5
1c	9.2	7.5	*Ca.* 4
3c	6.8	4.3	*Ca.* 2–4
4a	9.4	15	*Ca.* 4–5
4b	8.8	1.5	*Ca.* 4–5

lack of data shown for the enolization of **4b** in Figure 4 arises from the fact that, although consideration of the "gem effect"[25] might predict an increase in the rate of enolization, the rate of enolization of **4b** was in fact *ca.* one-tenth that of **4a** throughout the pH range investigated. Thus, the slower rate of enolization of **4b** precluded measurements at pH's appreciably below pK_{app}.

Discussion

It is apparent from this investigation that the commonly accepted practice of using the rapid iodination reaction as a trap for carbanion intermediates leaves much to be desired. It is possible to minimize the various side reactions between triiodide and buffer by operating under zero-order conditions, *i.e.*, low concentration of triiodide. Under these conditions a blank reaction is observed between buffer and triiodide,[7] and this can be subtracted from the change in OD caused by the reaction of interest between substrate and triiodide. However, these conditions are such that the substrate is present in concentrations anywhere from 100 and 1000 greater than triiodide, and as a result, less than 1% of the substrate is reacting with the triiodide. The presence of minute amounts of reactive impurities could lead to nonlinear traces and highly questionable kinetic data. This type of problem has been observed in some earlier investigations of the enolization process.[7,9] If the concentration of ketone is decreased and triiodide increased sufficiently to assure pseudo-first-order conditions, the extraneous reaction between buffers and triiodide becomes competitive with the reaction of interest. It is difficult to understand, for example, how Harper and Bender[9] were able to use phosphate buffer for such a large portion of the pH range of their investigation. From our results, the production of triiodide ion from iodide ion in the presence of potassium hydrogen phosphate precludes the use of this buffer with triiodide. The stoichiometry of the iodination reaction in this research (*ca.* 2–5 mol of iodine per mole of ketone) is not unreasonable if one considers the fact the initial product of iodinating a β-amino ketone at the α-carbon is a β-iodamine (*i.e.*, a type of nitrogen mustard). This product could then react rapidly to form aziridinium compounds, capable of eliminating and undergoing further iodination, such as depicted in eq 2.

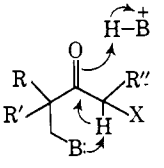
From the data presented in Figures 1–4, it is obvious that intramolecular participation by the β-amino group is observed in the enolization reaction. The pK_{app}'s (Table III) obtained from the kinetic data are in good agreement with the amine pK_a's determined experimentally (Table I). Thus, the ionizable group which is responsible for the observed pH–log rate profiles is the



(2)

β-amino moiety. The work of Bender and Williams[7] represents the only investigation of the amine-catalyzed enolization of ketones. The only ketone used in their study was acetone, and thus, a comparison between intramolecular catalysis by amines can be made only for **1a**, a Mannich base of acetone. Ignoring the small differences in temperature between the two investigations (25 *vs.* 30°), comparison of the general-base rate constant for trimethylamine-catalyzed enolization of acetone with the intramolecular catalysis in **1a** leads to $k_{intra}/k_{inter} = 7.9 \times 10^{-2}$ min^{-1}/1.57 M^{-1} min^{-1} $\simeq 5 \times 10^{-2}$ M. Thus, at 5×10^{-2} M trimethylamine, k_{obsd} for enolization of acetone is that of the plateau rate of **1a**. This is a considerably smaller equivalent concentration than is normally associated with intramolecular catalysis (see ref 3a, p 119). The intramolecular catalysis reported by Harper and Bender[9] in the enolization of *o*-isobutyrylbenzoic acid appears to be much larger than that found in this research. However, the pH dependence of the keto–lactol equilibrium[10] complicates the system. It was concluded that the titration curve obtained on plotting k_{obsd} *vs.* pH (Figure 1, ref 9) indicated participation by the *o*-carboxylate anion in the enolization reaction. In fact, the observed pH dependence could be explained equally well by assuming a preequilibrium between the keto and lactol forms. As pH is increased, the nonreactive lactol form is transformed to the reactive keto form which is free to enolize, resulting in an increase in k_{obsd}. Thus, although the plateau rate observed by Harper and Bender[9] is most probably due to intramolecular catalysis by the *o*-carboxyl group, a quantitative measure of this catalysis must take into account the effect of the keto–lactol equilibrium.

Catalysis by a general base such as is proposed on the basis of eq 1 is depicted by (3). However, the fact that the Mannich base derived from pinacolone (**1c**) dis-



(3)

plays the same type of pH–log rate profile as **1a** makes this mechanism not generally applicable to all β-amino ketones in Chart I. It is possible that the general base could operate on the other α-proton as in (4), either directly (4a) or through a water molecule (4b). Mechanism 4a would appear sterically less likely than mechanism 4b since inspection of Stuart–Briegleb molecular models indicates that the nitrogen lone pair does not overlap appreciably with the C–H σ bond. On the other hand a Grotthaus-type mechanism as (4b) is presently considered unfavorable for carbanion formation.[26]

(25) T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, 90, 3808 (1968), and references therein.

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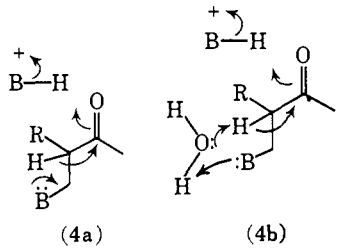
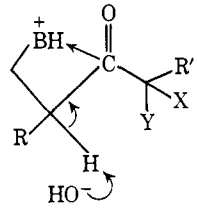


(4a) (4b) (4)

Another alternative to (3) is the kinetically equivalent intramolecular general-acid, specific-base catalysis



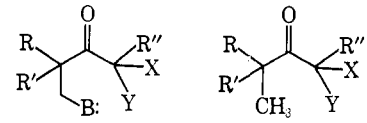
(5)

such as depicted by (5). This type of catalysis gives rise to the rate expression 6. Comparison of eq 6 and eq 1 leads to eq 7. Evaluation of k_b' for **1a** and **1c** gives

$$k_{obsd} = k_b'[HO^-]\frac{a_H}{K_a + a_H} = k_b'\frac{K_\omega}{K_a + a_H} \quad (6)$$

$$k_b = k_b'\frac{K_\omega}{K_a} \quad (7)$$

k_b' of *ca.* 10^3 min^{-1}, whereas for **3c**, $k_b' \approx 10^5$ min^{-1}. These rate constants are not unreasonable, and although Bender and Williams[7] did not observe any general-acid catalysis of the enolization of acetone by the conjugate acid of trimethylamine, such a pathway cannot be ruled out for all enolization reactions. The mechanism of Bender and Williams[7] involved formation of a ketimine intermediate catalyzed by ammonium ions. However, this is not the only possible mechanism for this type of catalysis. In our investigation, the use of a tertiary amine as an intramolecular general base was dictated by the desire to avoid possible cyclic ketimine formation between the β-amino group and the carbonyl. It may be that the quaternary ammonium ions of the Mannich bases investigated in this research, unable to form ketimines, act by a different mechanism than proposed for ammonium ions of primary and secondary amines in the enolization of acetone.[7] This is not without precedent, as Westheimer and Cohen[27] found that the dealdolization of diacetone alcohol is catalyzed by primary and secondary amine, but not tertiary amines, a fact they ascribed to formation of ketimine intermediates. More recently, however, Gutsche and coworkers[28] have shown that general-base catalysis by tertiary amines is involved in the aldol condensation of 2 mol of glyceraldehyde *via* the path glyceraldehyde → dihydroxyacetone → hexoses. The critical difference is that the latter reaction involves abstraction of the α-proton from glyceraldehyde by a general base, whereas the dealdolization reaction involves a specific reaction to form a ketimine intermediate. Thus, it is not inconceivable that ketimine formation is the means by which the conjugate acids of primary and secondary amines catalyze the enolization of acetone,[7] whereas in the present research where no such ketimine formation is possible, an intramolecular general-acid, specific-base mechanism might be operative. Depending upon the position of the proton between oxygen and B in eq 5, assistance may be viewed as either general-acid catalysis or electrostatic stabilization of the incipient negative charge developing on the carbonyl oxygen in the transition state. It is possible to compare the plateau rates, k_b (Table III), for the β-amino ketones (**7a**) with the hydroxide-catalyzed rate of enolization[29] for some of the corresponding alkyl ketones (**7b**). If this type of comparison is carried out at



7a 7b

a pH equal to the pK_a of the related β-amino ketone, rate enhancements of between 10^2 and 10^3 are obtained.

From the data of Figure 4, it can be stated that there is no evidence for a push–pull catalysis in the enolization of **4a** and **4b**. Such a concerted mechanism would be expected to give the familiar "bell-shaped" pH–rate profiles (see ref 3a, p 14). Since for α,ω-diamines of type **4**, p$K_{a_1} \cong$ pK_{a_2},[12b] the pH maximum for the "bell-shaped" profile would be at pK_{app}. This is obviously not seen for **4a** and **4b**. It might be argued that the hydroxide-catalyzed (k_{OH}) enolization of **4a** and **4b** could become dominant as the pH is increased above pK_{app}. In the limited pH range of this investigation, the k_{OH} term might prevent observation of any decrease in k_{obsd} as the pH is increased above pK_{app}. However, comparison of the plateau rates (k_b) for enolization of **4a** and **4b** with k_{OH} for the corresponding alkyl ketones, **7b**,[29] reveals that at pH 10, k_{OH} contributes less than 1% to k_{obsd} for **4b** and less than 0.1% to k_{obsd} for **4a**. This value of pH is considerably above pK_{app} (Table III) where a maximum in the profile should be observed for a concerted mechanism. Lienhard and Anderson[30] observed no enhanced catalytic effect of dicarboxylic acids compared with monocarboxylic acids in the enolization of acetone. Likewise, it must be concluded that the enolization of **4a** and **4b** can be described by eq 1 and that the intramolecular catalysis shown by these diamines is the same as that exhibited by the monoamines **1** and **3**.

Acknowledgment. This work was supported by Grant GB 5294X from the National Science Foundation.

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(28) C. D. Gutsche, R. S. Buriks, J. Nowotny, and H. Grassner, *ibid.*, **84**, 3775 (1962).

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(30) G. E. Lienhard and F. H. Anderson, *J. Org. Chem.*, **32**, 2229 (1967).