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Base-Catalyzed β-Elimination Reactions in Aqueous Solution. I. Elimination from β-Acetoxy Ketones

Leo R. Fedor

Contribution from the Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214.

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Abstract: 4-Methyl-4-acetoxy-2-pentanone reacts with tertiary amines and with hydroxyl ion in aqueous solution to form 4-methyl-3-penten-2-one. Reactivity of the bases is related to their pK_a by the Brønsted relationship, log $k_2 = 0.46\text{p}K_a - 5.0$. Negative deviations of rate constants from this equation are presumed due to steric inhibition of proton abstraction, a conclusion supported by the greater reactivity of 4-acetoxy-2-butanone with hydroxyl ion.

Several biologically important reactions may be classified formally as β-elimination reactions and are represented by eq 1.[1] A particular example of

$$\underset{\mathbf{1}}{\text{RCHX—CHY—CO—R}_1} \rightleftharpoons \underset{\mathbf{2}}{\text{RCH=CY—CO—R}_1} + \text{HX} \quad (1)$$

such reactions is the enzyme-mediated interconversion of D-(−)-β-hydroxybutyryl-ACP and crotonyl-ACP in fatty acid biosynthesis in *E. coli.*[2] Although the over-all sequence of reactions in fatty acid biosynthesis has been established, very little is known of the chemical mechanism employed by enoyl hydrase in mediating the interconversion of hydroxybutyrate and crotonate.[3]

Catalysis by hydronium ion[4–11] and by hydroxyl ion[12–14] of nonenzymic reversible dehydrations of β-hydroxycarbonyl compounds (eq 1: **1**, X = OH; Y = H)[15] is well established. Also, intramolecular carboxyl group catalysis of hydration of fumaric acid[16] as well as general acid catalysis of hydration of type **2** compounds are known.[11,17] The preceding establishes hydronium ion and hydroxyl ion catalysis as well as general acid catalysis of hydration–dehydration reactions of type **1** and type **2** compounds. However, general base catalysis of elimination from type **1** compounds by amine bases in aqueous solution has not been established although such catalysis is predictable on the basis of previous investigations.[18]

Since many enzymic reactions are believed to be catalyzed in a Brønsted general base sense by functional groups of the protein, it was of interest to determine if type **1** compounds (eq 1) undergo nonenzymic general base catalyzed β elimination. An experimentally convenient compound for such a study is 4-methyl-4-acetoxy-2-pentanone (**3**) which undergoes base-catalyzed β elimination, forming 4-methyl-3-penten-2-one (**4**).[22] The β-acetoxy ketone is not labile to retrograde aldol-type condensation as is the parent 4-methyl-4-hydroxy-2-pentanone (**5**) since **3** does not possess the requisite acidic alcohol group.[14,25] Further, acetyla-

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[16] M. L. Bender and K. A. Connors, *J. Am.. Chem. Soc.*, **84**, 1980 (1962).

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[18] General base catalysis in elimination reactions of compounds structurally dissimilar to type 1 compounds is well known. Thus Crowell and Francis[19] and Kim[20] have established general base catalysis by acetate ion and hydroxyl ion in the solvolysis of 3,4-methylenedioxy-β-nitrostyrene. Similarly, Weinstock, Pearson, and Bordwell[21] have established general base catalysis by trimethylamine, triethylamine, and piperidine in *cis* and *trans* eliminations in the cyclopentane and cyclohexane series.

[19] T. I. Crowell and A. W. Francis, *J. Am. Chem. Soc.*, **83**, 591 (1961).

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tion of **5** introduces a better leaving group into the molecule (pK_a of acetic acid = 4.6 *vs.* pK_a of water = 15.57), a type of modification an enzyme might reasonably effect in the dehydration of β-hydroxybutyryl-ACP. Ketone **3** was chosen rather than a suitably substituted thiol ester because of the known lability of the thiol ester bond to aminolysis and because the ketone group resembles the thiol ester group with respect to its influence on the acidity of hydrogen atoms on carbon α to that group.[26]

Experimental Section

Reagents. Inorganic salts were Baker Analyzed reagent. Organic reagents were purchased from Distillation Products Industries and were recrytallized or distilled before use. Tap distilled water was redistilled through a Corning AG-1a still before use. 4-Acetoxy-4-methyl-2-pentanone was prepared by the method of Gault and Lumbroso,[27] bp 35° (0.5 mm) (lit.[27] bp 78° (18 mm)). 4-Acetoxy-2-butanone was prepared by the method of Hoffman and co-workers,[28] bp 77–79° (9 mm) (lit.[28] bp 92–95° (25 mm)). Dioxane was purified by the method of Fieser.[29] Standard buffer solutions were purchased from A. H. Thomas Co.

Apparatus. A Gilford Model 2000 spectrophotometer was used for kinetic measurements. The cell compartment was thermostated by circulating water of constant temperature (±0.1°) through thermospacers. pH measurements were made on a Heath Model 301 pH meter equipped with a Thomas No. 4858-L60 combination electrode. Ultraviolet spectra were scanned using a Perkin-Elmer Model 4000A spectrophotometer.

Kinetics. The courses of the reactions of 4-methyl-4-acetoxy-2-pentanone (**3**) and of 4-acetoxy-2-butanone (**6**) to give 4-methyl-3-penten-2-one (**4**) and 3-buten-2-one (**7**) were monitored at 243[10] and at 225 mμ, respectively. Because of the high absorbance of concentrated amine solutions at low wavelength the production of **4** was occasionally monitored at wavelengths higher than 243 mμ. All reactions were carried out in water solutions at 30 ± 0.1° and at a calculated ionic strength of 1.0 *M* with KCl unless otherwise specified. The tertiary amines used in this study supplied their own buffer capacity, and the pH's of all solutions were determined before each run and occasionally after some runs to ensure constancy of pH (±0.02 unit). Cuvettes (3 ml) were filled to the stopper level with the appropriate solution, capped, and allowed to come to thermal equilibrium. Reactions were started by adding a known amount of **3** or **6** in methanol *via* a micropipet to the solution in the cuvette and stirring with a polythene paddle. Reactions were carried out under pseudo-first-order conditions (concentration of **3** or **6** *ca.* 5×10^{-5} *M*), and pseudo-first-order rate constants were obtained by multiplying slopes of plots of log $((\mathrm{OD}_\infty - \mathrm{OD}_{\mathrm{initial}})/(\mathrm{OD}_\infty - \mathrm{OD}_{\mathrm{time}}))$ *vs.* time by 2.303. Reactions were monitored for at least three half-lives and pseudo-first-order plots were nearly always linear to at least two half-lives. Pseudo-first-order plots for imidazole-catalyzed reactions of **3** showed upward curvature due to unstable OD_∞ values, possibly due to catalyzed hydration of **4**.[30,31] Pseudo-first-order plots were linear to one half-life, and the second-order rate constant for this reaction (Table I) is believed to be a good approximation to the correct value. The activity of hydroxyl ion was calculated from K_w/a_H wherein K_w is the autoprotolysis constant for water ($-\log K_w = 13.83$ at 30°)[34] and a_H is the activity of the hydrogen ion determined with the glass electrode. For 50% (w/w) dioxane–water solution $-\log K_w = 15.85$, by extrapolation from the data of Harned and Fallon.[35]

Product Analysis. The courses of the reactions of 4-methyl-4-acetoxy-2-pentanone (**3**) with tertiary amines and with hydroxyl ion were scanned from 230 to 300 mμ. Only the appearance of a peak at 243 mμ (4-methyl-3-penten-2-one (**4**)) was observed. A quantitative determination of the amount of **4** formed from **3** in tertiary amine buffers at pH 9.15 and 11.15 was made using authentic **4** for comparison. Conversion of **3** to **4** was quantitative.

Isolation of 4. **3** (0.5 g) was treated with 4 ml of 1 *M* KOH. After 10 min solid sodium sulfate was added to the basic reaction mixture, the mixture was extracted with ether, and the ethereal extract was dried over anhydrous sodium sulfate. Evaporation of the ether gave 0.125 g of **4**, identified by infrared spectral comparison with authentic **4**.

2,4-Dinitrophenylhydrazone of 4. **3** (0.5 g) was treated with 4 ml of 1 *M* potassium hydroxide in 3 ml of dioxane. After 10 min solid sodium sulfate was added to the solution, the mixture was extracted with ether, and the ethereal extract was dried over anhydrous sodium sulfate. Evaporation of the ether left a liquid residue which was dissolved in 95% ethanol to make 10 ml of final volume. A 5-ml portion of this solution was added to 0.4 g of 2,4-dinitrophenylhydrazine in 2 ml of H_2SO_4, 3 ml of H_2O, and 10 ml of 95% ethanol.[36] The precipitated solid, 0.23 g (55.2%), was crystallized from ethyl acetate–95% ethanol to give crimson-colored needles, mp 202.5–203.5°. An authentic sample of the 2,4-dinitrophenylhydrazone of **4** had mp 202.5–203.5° (lit. mp 200°,[36] 203°[37] (carmine)). The mixture melting point was not depressed.

Results

The β elimination of acetic acid from 4-methyl-4-acetoxypentan-2-one (**3**) to give 4-methyl-3-penten-2-one (**4**) in aqueous solutions of tertiary amines is general base catalyzed. At constant pH (30°, μ = 1.0 with KCl) the formation of **4** is given by eq 2. Under

$$d(\mathbf{4})/dt = (k_{\mathrm{OH}}(\mathrm{OH}^-) + k_2'(\mathrm{R_3N_{total}}))(\mathbf{3}) \qquad (2)$$

pseudo-first-order conditions, $k_{\mathrm{obsd}} = k_{\mathrm{OH}}(\mathrm{OH}^-) + k_2'(\mathrm{R_3N_{total}})$ and graphical plots of k_{obsd} *vs.* $(\mathrm{R_3N_{total}})$ are linear with slope k_2' and intercept $k_{\mathrm{OH}}(\mathrm{OH}^-)$ (Figure 1). Second-order rate constants, k_2, were obtained by dividing k_2' by the mole fraction of total amine present as free amine, $K_a'/(K_a' + a_H)$, and are given in Table I. The constant k_{OH} was evaluated graphically from the slope of a plot of k_{obsd} *vs.* K_w/a_H for reactions of **3** with potassium hydroxide solutions (Table I, Figure 2). The constant k_{OH} for the reaction of 4-acetoxy-2-butanone (**6**) with potassium hydroxide was similarly evaluated (Table I, Figure 2). An additional term for a water-catalyzed reaction may be involved in eq 2.[38]

The reactivity and sensitivity of **3** to base catalysis is provided by the Brønsted equation, $\log k_2 = 0.46\mathrm{p}K_a' - 5$, which was obtained from a plot of log k_2 *vs.* pK_a

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(30) Bell and his co-workers[10] have demonstrated general acid catalysis of hydration of **4** by polyprotic acids.

(31) Imidazole does not form addition compounds with aldehydic groups[32] suggesting it behaves as a tertiary amine. Further support for this suggestion is found in the fact that N-methylimidazole is about as reactive as imidazole in nucleophilic displacement reactions toward *p*-nitrophenyl acetate.[33]

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(38) The contribution of a water-catalyzed reaction to the over-all rate at higher pH values with amines of higher pK_a is negligible (undetectable). However, for three reactions of **3** with N-methylmorpholine, the stoichiometric concentrations of amine, the pH of the reaction solutions, and the pseudo-first-order rate constants (min^{-1}) are: 0.04 *M*, 8.82, 8.55×10^{-4}; 0.10 *M*, 8.80, 9.60×10^{-4}; 0.20 *M*, 8.84, 13×10^{-4}. For the 0.2 *M* solution approximately 50% of the reaction is hydroxyl ion catalyzed and 40% is amine catalyzed. The residual rate may be attributed to a water reaction (Table I). Further, a plot of $(k_{\mathrm{obsd}} - k_{\mathrm{OH}} \cdot (\mathrm{OH}^-))$ *vs.* the concentration of free triethylenediamine for the reaction of **3** with this amine ($12k_{\mathrm{obsd}}$) is linear and similarly gives a small intercept which may be interpreted as a water reaction.

Table I. Rate Constants for the Reaction of Tertiary Amines and Hydroxyl Ion with 4-Methyl-4-acetoxy-2-pentanone (**3**) and for the Reaction of Hydroxyl Ion with 4-Acetoxy-2-butanone (**6**) (Solvent H_2O, 30°, μ = 1.0 with KCl)

Reagent	Ketone	k_2 or k_{OH}, M^{-1} min^{-1}	pK_a' [a]	pH range	Concn range of reagent	No. of runs
Water	**3**	2.0×10^{-6} [b]	−1.7			
Imidazole	**3**	1.6×10^{-2} [c]	7.1	7.62–9.17	0.1–1.0	12
N-Ethylmorpholine	**3**	. . . [d]	7.7	10.02–10.10	0.04–0.50	5
N-Methylmorpholine	**3**	3.0×10^{-3}	7.7	8.80–8.84	0.04–0.20	3
Triethylenediamine	**3**	2.2×10^{-1}	9.15	9.15–9.72	0.08–1.0	12
N,N,N′,N′-Tetramethylethylenediamine	**3**	5.2×10^{-2}	9.45	10.0	0.1–1.0	6
Trimethylamine	**3**	7.8×10^{-1}	10.0	10.0–10.55	0.02–0.60	23
Trimethylamine	**3**	7.4×10^{-1} [e]	10.0	9.80	0.02–0.10	5
Trimethylamine	**3**	5.8×10^{-2} [f]	9.20	9.20	0.02–0.10	6
Triethylamine	**3**	7.4×10^{-2}	11.00	10.03–10.92	0.05–1.0	20
Hydroxide ion	**3**	6.4×10	15.57 [g]	11.07–11.61	0.003–0.01	9
Hydroxide ion	**3**	2.65×10^{2} [f]		11.98–13.09	0.001–0.01	5
Hydroxide ion	**6**	5.2×10^{2}	15.57 [g]	10.55–11.32	0.001–0.004	6

[a] Determined by the method of half-neutralization. [b] ($k_{obsd} - K_{OH}(OH^-)$) divided by 55.5 M for the reaction of **3** in N-methylmorpholine buffer (see Results). [c] See Experimental Section. [d] No catalysis detectable above the hydroxyl ion catalyzed reaction. [e] Ionic strength = 0.1. [f] Determined in 50% (w/w) aqueous dioxane, μ = 0.1. [g] $-\log(K_w/55.5)$.

(Figure 3) for the reaction of **3** with hydroxyl ion, trimethylamine, triethylenediamine, imidazole, and water. The k_2 and K_a values for diamines were corrected for statistical factors. The second-order rate constants for reactions of **3** with N-methylmorpholine, N,N,N′,N′-tetramethylethylenediamine, and triethylamine show marked negative deviations from the Brønsted equation (Figure 3), and no catalysis by N-ethylmorpholine was detected under the experimental condition used (Table I). A tenfold change in ionic strength (0.1–1.0 M) did not affect the rate of the general base catalyzed reaction of **3** with trimethylamine, and the hydroxyl ion catalyzed rate in this amine buffer (μ = 0.1) was correctly predicted using k_{OH} determined for μ = 1.0. Changing the solvent composition from water to 50% aqueous dioxane resulted in a decrease in the value of k_2 for the trimethylamine-catalyzed conversion of **3** to **4** and an increase in the value of k_{OH} for the hydroxyl ion catalyzed conversion of **3** to **4** (Table I).

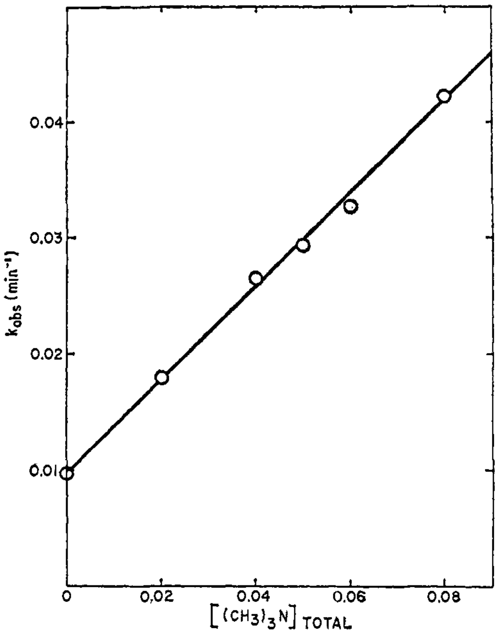


Figure 1. Plot of pseudo-first-order rate constants, k_{obsd}, *vs.* total trimethylamine concentration for the reaction of **3** with that amine (pH 10.01, 30°, μ = 1.0 with KCl). The slope of the line is k_2', the apparent second-order rate constant for reaction of the amine with **3**, and the intercept is $k_{OH}(OH^-)$, the concentration-dependent apparent first-order rate constant for reaction of hydroxyl ion with **3**.

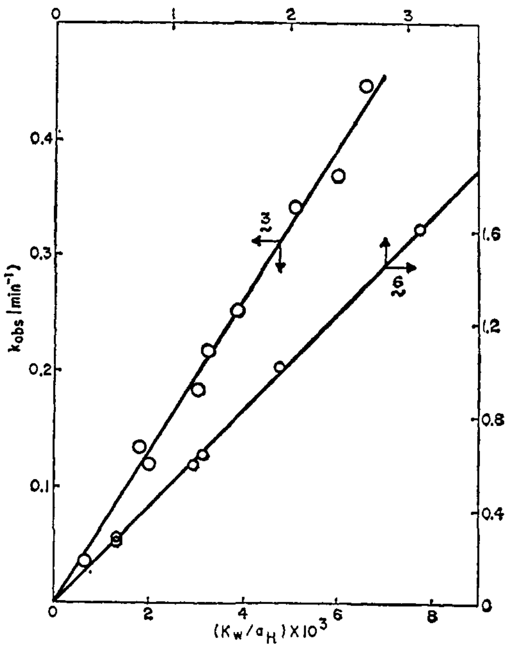


Figure 2. Plot of the pseudo-first-order rate constants, k_{obsd}, *vs.* K_w/a_H for the reaction of hydroxyl ion with **3** (left ordinate, bottom abscissa) and with **6** (right ordinate, top abscissa) (30°, μ = 1.0 with KCl). The slope of the line is k_{OH} (Table I).

Discussion

The reaction of **3** to give **4** is general base catalyzed by hydroxyl ion and by some tertiary amines. The reactivity and sensitivity of **3** toward base catalysis is provided by the above Brønsted equation (Figure 3). Appreciable negative deviations of rate constants from this equation are presumed due to steric hindrance of proton abstraction from **3** by amines as triethylamine,

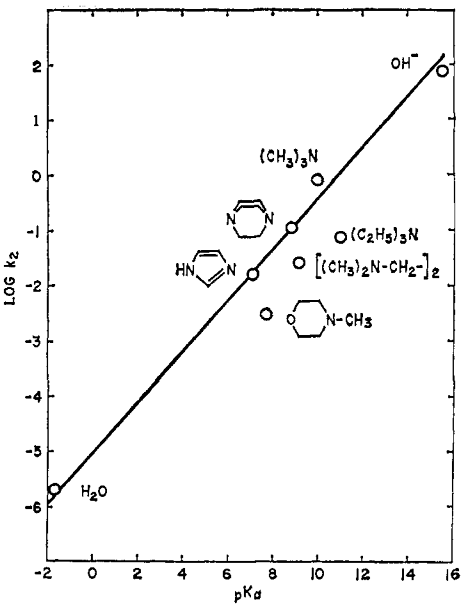


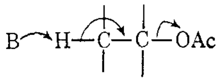
Figure 3. Plot of the logarithm of the second-order rate constant for reaction of general bases with **3** *vs.* pK_a of the conjugate acid of the appropriate base. The rate constants for reaction of the diamines with **3** have been halved and the corresponding K_a values doubled to correct for statistical factors. The slope of the line is $\beta = 0.46$ ($s_\beta = 0.057$, $r = 0.98$).

N,N,N′,N′-tetramethylethylenediamine, and N-alkylmorpholines. Weinstock, Pearson, and Bordwell[21] similarly observed that triethylamine is a poorer general base catalyst than is trimethylamine in elimination reactions and attributed this result to steric factors. Gutsche and his co-workers[39] have shown that the general base catalyzed aldol condensation of D-glyceraldehyde to give D-fructose and D-sorbose by pyridine bases is sensitive to the steric environment around nitrogen. The base here functions as a proton acceptor. In the present study, additional support for the steric hindrance thesis is provided by the eightfold greater reactivity of **6** than **3** toward hydroxyl ion (Table I).

It is anticipated that the structurally divergent bases water, trialkylamines, and hydroxyl ion should approximate a Brønsted relationship since the effectiveness of a catalyst in a proton abstraction reaction should be proportional to the pK_a of the catalyst provided steric effects are not important and provided solvation differences are not great. Thus basic catalysis of the mutarotation of glucose[40] as well as general base catalysis of hydrolysis of acyl-activated oxygen esters[41] and ethyl trifluorothiolacetate[42] provide examples of reactions wherein structurally different bases fit a single Brønsted equation.

The effects of solvent variation on the velocity of the amine and hydroxyl ion catalyzed elimination reactions of **3** are in opposite directions. The reaction of the neutral molecules trimethylamine and **3**, which presumably proceeds through a charge-separated transition state (Brønsted $\beta = 0.46$), is about 13-fold faster in water than in 50% aqueous dioxane (Table I). Thus the transition state is better stabilized in the solvent of higher dielectric constant. In contrast, the reaction of hydroxyl ion with **3** is about fourfold faster in 50% aqueous dioxane than in water (Table I). This reaction involves no change in charge in formation of the transition state and the effect of solvent is to increase the activity of hydroxyl ion through reduced solvation of that anion in the mixed solvent.[43,44]

General base catalysis of the conversion of **3** to **4** may be rationalized mechanistically on the basis of (1) an E2 reaction wherein the abstraction of a proton from **3** by the base B is concerted with the formation of the olefin bond and departure of the acetoxy group,



or (2) rate-limiting enolization of **3** followed by a rapid loss of acetate ion from $\mathbf{3}^-$.

$$\mathrm{B} + \mathbf{3} \underset{k_{-1}}{\overset{\text{slow}\atop k_1}{\rightleftarrows}} \mathbf{3}^- + \mathrm{BH}^+$$

$$\mathbf{3}^- \underset{\text{fast}}{\xrightarrow{k_2}} \mathbf{4} \qquad k_2 \gg k_{-1}$$

The ElcB mechanism involving rapid equilibration of **3** and $\mathbf{3}^-$ followed by a slow decomposition of the enolate anion $\mathbf{3}^-$ is precluded on the basis that such a mechanism predicts specific base catalysis only,[21] a result contrary to the present findings.

It is noteworthy that the hydroxyl ion catalysis of dehydration of 4-methyl-4-hydroxy-2-pentanone (**5**) proceeds with a second-order rate constant of *ca.* $4 \times 10^{-4}\ M^{-1}\ \mathrm{min}^{-1}$.[14] This value may be compared with the value 64 $M^{-1}\ \mathrm{min}^{-1}$ for hydroxyl ion catalysis of acetic acid elimination from **3**. The 10^5-fold rate enhancement in β elimination attending modification of the leaving group, while not unusual, may present an interesting implication for enzyme-catalyzed elimination reactions.

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