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Hydrolytic Reactions of 4(5)-Hydroxymethylimidazolyl Acetate, 1-Methyl-5-Hydroxymethylimidazolyl Acetate, 4(5)-Chloromethylimidazole, and 1-Methyl-5-chloromethylimidazole

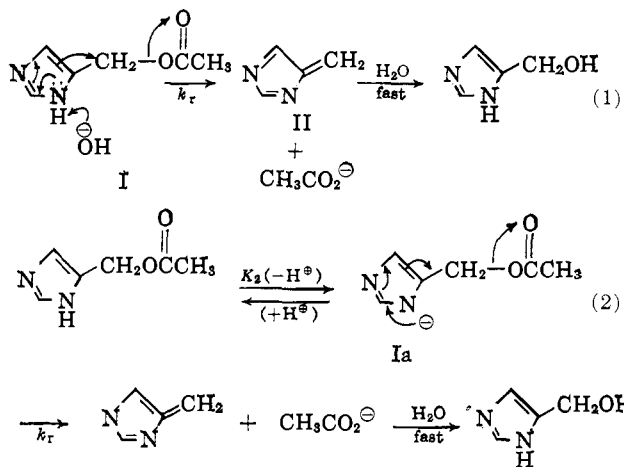
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RECEIVED MAY 4, 1964

In a previous study from this laboratory (Bruce and Fife), it was shown that 4(5)-hydroxymethylimidazolyl acetate (I) undergoes facile OH^\ominus catalyzed (k_{OH}) or general-base catalyzed (acetate, pyridine, imidazole) hydrolysis. From the magnitude of the rate constants, and the establishment that I undergoes facile alkyl-oxygen scission on reaction with nucleophiles, it was proposed that the mechanism(s) of hydrolysis involved proton abstraction and elimination of acetate ion with the formation of a metastable diazofulvene intermediate (II). Reanalysis of the original data has shown no contributions of an $\text{S}_{\text{N}}1$ nature to the solvolytic process. To determine if the hydroxide ion catalyzed hydrolysis proceeds through pre-equilibrium formation of an anion intermediate or *via* proton abstraction concerted with elimination of acetate ion, the deuterium solvent isotope effect was determined (80°). The ratio of $k_{\text{obsd}}^{\text{H}}/k_{\text{obsd}}^{\text{D}}$ was found, on the basis of the conductometrically determined $\text{p}K_2$ values for imidazole in H_2O and D_2O , to be more in accord with an anionic intermediate—true specific base-catalyzed elimination. The previous supposition of an elimination mechanism has found support in the observation that 1-methyl-5-hydroxymethylimidazolyl acetate (III), unlike the ester I, exhibits tendencies to only acyl-oxygen scission on reaction with nucleophiles (MeO^\ominus , NH_2OH). The aqueous hydrolysis of III (78° , pH 5.49 to 9.20) was found to occur with contributions from a spontaneous and an OH^\ominus catalyzed rate, whose deuterium solvent isotope effects were determined to be $k^{\text{H}}/k^{\text{D}} = 1.1$ and 0.58, respectively, in accord with intramolecular nucleophilic and $\text{B}_{\text{AC}}2$ catalyzed hydrolysis, respectively. Both reactions were found to be quite facile ($k_{\text{OH}} = 40$ to 220 times that for the alkaline hydrolysis of *p*- and *m*-nitrobenzyl acetates, respectively). The aqueous solvolysis of 4(5)-chloromethylimidazole (V) yields only 4(5)-hydroxymethylimidazole. The rate of solvolysis cannot be either an intramolecular $\text{S}_{\text{N}}2$ elimination of Cl^\ominus (the rate is much too fast when compared to the hydrolytic rates for nitrogen mustards) or an $\text{S}_{\text{N}}2$ attack of OH^\ominus (k_{OH} would approach a diffusion-controlled process). The reaction, therefore, must be an elimination of Cl^\ominus from the neutral base species. The ratio of the rate constants for the neutral solvolysis of V to the similar constant for 1-methyl-5-chloromethylimidazole (X) is 1:1.2, supporting an intermediate carbonium ion rather than a neutral diazofulvene intermediate. Further substantiation of an $\text{S}_{\text{N}}1$ mechanism for V is provided by the finding of a deuterium solvent isotope effect of $k^{\text{H}}/k^{\text{D}} = 1.25$, a value previously determined for the solvolysis of a *t*-butyl chloride. A common ion effect was observed in the solvolysis of V, further substantiating carbonium ion formation. The solvolytic rate constant for V is about that for chloromethyl ethyl ether.

Introduction

Bruce and Fife³ studied the alkaline hydrolysis of 4(5)-hydroxymethylimidazolyl acetate (I) and found that the reaction proceeded by alkyl-oxygen scission. "Normal" ester hydrolysis, except for some special cases (*e.g.*, as the acid-catalyzed hydrolysis of *t*-alkyl esters⁴ and the alkaline hydrolysis of some benzhydryl systems⁵), proceeds by acyl-oxygen scission. The



- (1) Career Investigator, National Institutes of Health.
 (2) Predoctoral fellow, National Institutes of Health. Part of the work to be submitted by J. L. Herz in partial fulfillment for the Ph.D. Degree, Cornell University.
 (3) T. C. Bruce and T. H. Fife, *J. Am. Chem. Soc.*, **83**, 1124 (1961).
 (4) *Cf.*, for example, C. A. Bunton and J. L. Wood, *J. Chem. Soc.*, 1522 (1955); V. R. Stimson and E. J. Watson, *ibid.*, 2848 (1954); W. von E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, **75**, 4733 (1953).
 (5) (a) M. P. Balfe, A. Evans, J. Kenyon, and K. N. Nandi, *J. Chem. Soc.*, 803 (1946); (b) M. P. Balfe, E. A. W. Downer, A. A. Evans, J. Kenyon, R. Poplett, C. E. Searle, and A. L. Tarnoky, *ibid.*, 797 (1946).

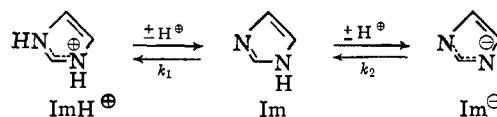
ester I was found to be subject to general-base-catalyzed hydrolysis by acetate ion, imidazole, and pyridine. A diazofulvene intermediate (II) was postulated. It was not determined, however, whether hydroxide ion itself acts as a general base (1) or as a specific base (2).

If (1) and/or (2) is the mechanism by which I hydrolyzes, substitution of the ionizable hydrogen by a methyl group should alter the mechanism of hydrolysis. It was also of interest to determine whether (1) or (2) is general for all derivatives of 4(5)-X-methyl-imidazoles regardless of the nature of X, or whether it is the mode of reaction for the hydrolysis of only derivatives where X- is a poor leaving group such as acetate ion.

Results and Discussion⁶

The kinetics of the hydrolysis of 1-methyl-5-hydroxymethylimidazolyl acetate (III) in water at 78° and

(6) Glossary of symbols used in this paper: k_{obsd} = observed pseudo-first-order rate at any constant pH; a_{H} = hydrogen ion activity as measured by the glass electrode; K_a = dissociation constant of a monobasic acid; K_1 and K_2 = first and second dissociation constants for a diprotic acid, *e.g.*, imidazole; $[\text{Im}_T] = [\text{ImH}^\oplus] + [\text{Im}] + [\text{Im}^\ominus]$; $[\text{ST}] = \text{stoichiometric}$



$$K_1 = \frac{[\text{Im}]a_{\text{H}}}{[\text{ImH}^\oplus]}, \quad K_2 = \frac{[\text{Im}^\ominus]a_{\text{H}}}{[\text{Im}]}$$

concentration of any substrate S; $[\text{ST}] = \sum_i [\text{S}_i]$; $[\text{S}_i] = [\text{SH}^\oplus]$, $[\text{S}]$, $[\text{S}^\ominus]$, etc.; K_w = autoprotolysis constant for H_2O ; $K_w = a_{\text{H}}[\text{OH}^\ominus]$; $K_{\text{D}_2\text{O}}$ = autoprotolysis constant for D_2O ; superscripts H and D refer to the various constants in H_2O and D_2O , respectively.

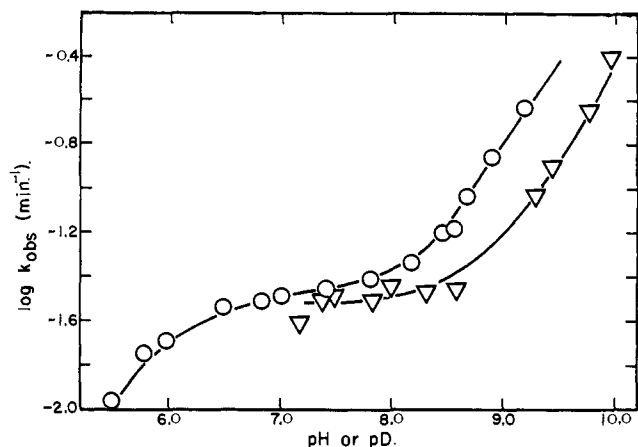


Fig. 1.—Log k_{obsd} -pH (and pD) profile for the hydrolysis of 1-methyl-5-hydroxymethylimidazolyl acetate (III) (78°, solvent water, $\mu = 1.0 M$).

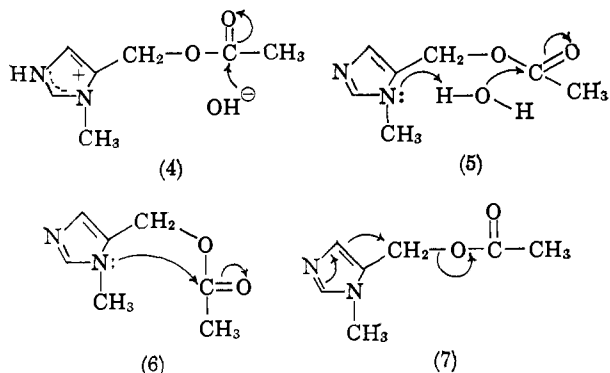
$\mu = 1.0 M$ (with KCl) were followed at constant pH on a pH-stat over the pH range 5.49 to 9.20. In Fig. 1 is plotted the logarithm of the observed pseudo-first-order rate constant (k_{obsd}) vs. pH. In the pH range studied, the reaction was found to be extremely facile. The value of the pseudo-first-order rate constant k_{obsd} at any pH is provided by 3. The values of k'_{OH} , k_{OH} ,

$$k_{\text{obsd}} = \frac{(\text{OH}^{\ominus})}{K'_{\text{app}} + a_{\text{H}}} [k'_{\text{OH}}a_{\text{H}} + k_{\text{OH}}K'_{\text{app}}] \quad (3)$$

$$= \frac{K'_{\text{app}}}{K'_{\text{app}} + a_{\text{H}}} [k_0 + k_{\text{OH}}(\text{OH}^{\ominus})]$$

and k_0 are the calculated second-order rate constants for attack of OH^{\ominus} on the conjugate acid and free base forms of III and the spontaneous rate of solvolysis of III, respectively. The value of K'_{app} is the kinetically apparent acid dissociation constant of the conjugate acid of III and was determined from an Eadie plot⁷ of the kinetic data. The points of Fig. 1 are experimental and the curve has been drawn employing the values of $k_0 = 3.34 \times 10^{-2} \text{ min.}^{-1}$ and $k_{\text{OH}} = 3.99 \times 10^2 \text{ l. mole}^{-1} \text{ min.}^{-1}$. The value of k_{OH} , when compared to the same constant for I,³ determined under the same conditions ($8.95 \times 10^4 \text{ l. mole}^{-1} \text{ min.}^{-1}$), indicates that a drastic decrease in the hydrolytic rate accompanies substitution of the active hydrogen of I by a methyl group to give III.

The hydrolytic reaction for III occurring at low pH values (*i.e.*, k_{OH} or k_0) may pertain to: (a) a normal $\text{B}_{\text{AC}2}$ hydrolysis of the conjugate acid of III as in (4);



(7) T. C. Bruce and J. M. Sturtevant, *J. Am. Chem. Soc.*, **81**, 2860 (1959); T. C. Bruce, *ibid.*, **81**, 5444 (1959).

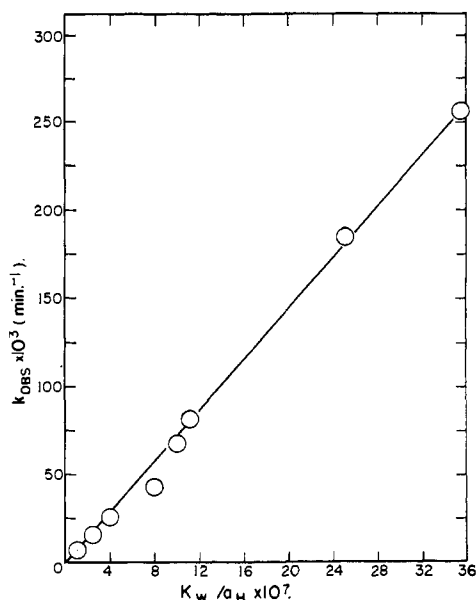


Fig. 2.—Plot of k_{obsd} vs. K_w/a_{H} for the hydrolysis of 4(5)-hydroxymethylimidazolyl acetate (I) (78°, solvent water, $\mu = 1.0 M$).

(b) an intramolecular general-base-catalyzed hydrolysis as in (5); (c) an intramolecular nucleophilic catalysis as in (6); or conceivably a carbonium ion mechanism as in (7).

Imidazole has been found to act as a general-base catalyst in the hydrolysis of various esters.^{8a} and as an intramolecular nucleophilic catalyst for the hydrolysis of esters of 4(5)-(hydroxyethyl)imidazole.^{8b}

The probability of a spontaneous elimination of acetate ion from III to yield a carbonium ion (7) as an explanation for the results of the pH-rate profile at low pH is readily discounted. If III undergoes carbonium ion formation during hydrolysis then compound I should do the same. In fact, compound I might be anticipated to afford a carbonium ion at the same rate as III.⁹ If formation of a carbonium ion makes a contribution to the over-all rate for the hydrolysis of I, then the observed rate constant should be equal to the sum of the rate constants for anionic elimination and carbonium ion formation (k^+). Under the conditions

$$k_{\text{obsd}} = k^+_{\text{carbonium ion}} + k_{\text{elimination}} \quad (8)$$

$$k_{\text{obsd}} = \left[k^+ + \frac{k_r k_2}{a_{\text{H}}} \right] \left[\frac{K_1}{K_1 + a_{\text{H}}} \right]$$

employed $K_1 \gg a_{\text{H}}$ so that 8 simplifies to 9.

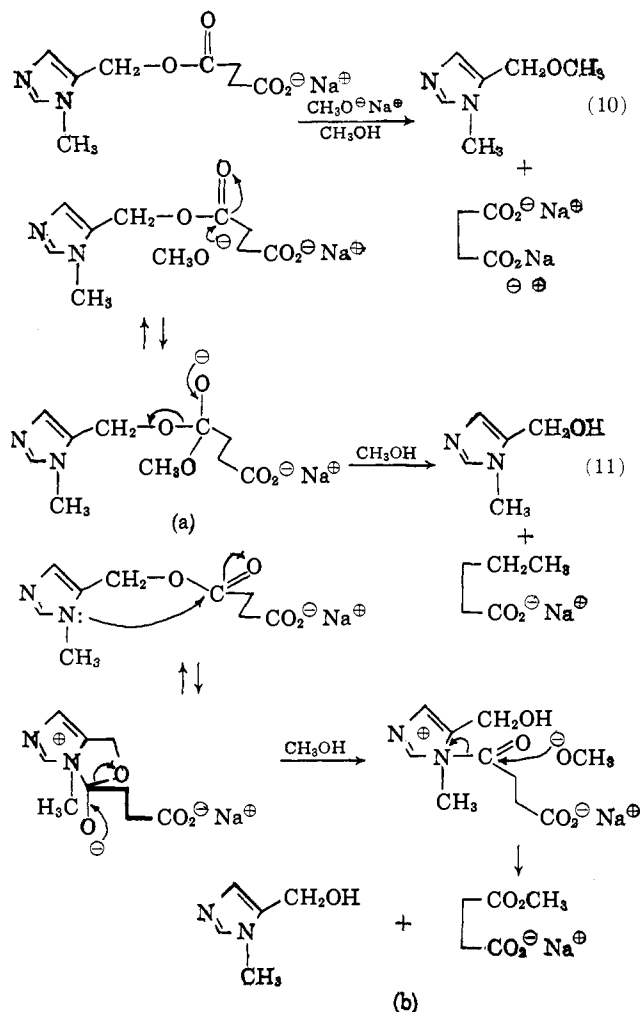
$$k_{\text{obsd}} = k^+ + (k_r K_2/a_{\text{H}}) \quad (9)$$

A plot of k_{obsd} vs. K_w/a_{H} should give a straight line of slope $k_r K_2/K_w$ and of intercept on the k_{obsd} axis of k^+ . In Fig. 2 is plotted k_{obsd} vs. K_w/a_{H} using the data of Bruce and Fife.¹ Inspection of the plot of Fig. 3 reveals that the intercept of the line on the k_{obsd} axis is at zero. From this one may infer that there is no contribution from a carbonium ion mechanism in the hydrolysis of III.

(8) (a) T. C. Bruce, T. H. Fife, J. J. Bruno, and P. Benkovic, *ibid.*, **84**, 3012 (1962); (b) U. K. Pandit and T. C. Bruce, *ibid.*, **82**, 3386 (1960).

(9) 1-Methyl-5-chloromethylimidazole (X) and 4(5)-chloromethylimidazole (V), which both form carbonium ions, hydrolyze at the same rate—this study.

To ascertain if III is susceptible to alkyl-oxygen cleavage on attack by base the half succinate ester of 1-methyl-5-hydroxymethylimidazole (IV) was subjected to alkaline methanolysis and III was allowed to react with hydroxylamine in aqueous solution. 1-Methyl-5-hydroxymethylimidazolyl hydrogen succinate (IV) was solvolized in methanol containing 2 equivalents of methoxide ion, 1 equivalent being used to react with the carboxyl group of the ester to form the sodium salt. If there is alkyl-oxygen cleavage, disodium succinate would be formed (10). If, on the other hand, the reaction proceeds *via* acyl-oxygen scission (11a,b), the sodium salt of monomethyl succinate would be isolable.



The experiment was performed in the following manner: 2 equivalents of sodium methoxide was added to a solution of ester in absolute methanol. The solution was sealed from the air and stirred in a nitrogen atmosphere for 3 hr. whereupon a large excess of anhydrous ether was added. The salt was filtered and dried, and an infrared spectrum was taken. This was superimposable on the spectrum of an authentic sample of the sodium salt of monomethyl succinate. The isolation of monomethyl succinate indicates acyl-oxygen scission for specific base methanolysis of VI, and one would expect the same behavior for III.

When III was treated with hydroxylamine in aqueous solution near neutrality a 92.5% yield of acethydroxamic acid was obtained. When I, which was shown to undergo alkyl-oxygen scission, is treated with hydroxyl-

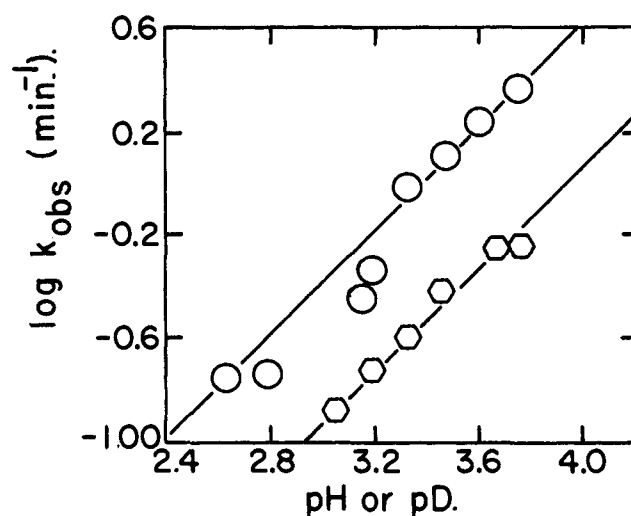


Fig. 3.—Log k_{obs} -pH (and pD) profile for the hydrolysis of 4(5)-chloromethylimidazole (30°, solvent water, $\mu = 1.0 M$).

amine under these same conditions, only a 20% yield of acethydroxamic acid is obtained.¹ The reaction of III with hydroxylamine, therefore, proceeds predominantly by acyl-oxygen scission.

Mechanisms (4), (5), and (6) remain as possible explanations for the "spontaneous" hydrolysis of III. Mechanism (5) entails a concerted proton abstraction from water, accompanying its attack on the carbonyl carbon in the rate-determining step and a kinetic solvent isotope effect (k^H/k^D) of at least 2 would be expected.⁸ Nucleophilic catalysis by imidazole (6), however, is known to proceed without a kinetic solvent isotope effect¹⁰ and for a $B_{AC}2$ mechanism (4) the isotope effect should be considerably smaller than 1.0. Included in Fig. 1 is a plot of $\log k_{\text{obs}}$ vs. pD for the hydrolysis of III in D_2O . The straight line portion of the curve, having a slope of 1.0, is shifted over to the left from the line in H_2O because the autoprotolysis constant for D_2O is about 1/6 of that for H_2O . The observed pseudo-first-order rate coefficient obeys the expression

$$k_{\text{obs}} = \left[\frac{K_a^D}{K_a^D + a_D} \right] [k_0^D + k_{OD}(OD^\ominus)] \quad (12)$$

where $k_0^D = 2.93 \times 10^{-2} \text{ min.}^{-1}$ and $k_{OD} = 6.87 \times 10^2 \text{ l. mole}^{-1} \text{ min.}^{-1}$. A glass electrode correction¹¹ to the pH meter reading was made to obtain pD, and the concentration of OD^\ominus was calculated assuming that K_w/K_{D_2O} is the same at 78° as it is at 30°. The determined kinetic solvent isotope effect $k_0^H/k_0^D = 3.34 \times 10^{-2}/2.93 \times 10^{-2} = 1.1$, is in keeping with (6). In addition, a $B_{AC}2$ mechanism involving the conjugate acid of III as in (4) may be firmly ruled out. Thus, it is known that the electrostatic facilitation of a trimethylammonium ion substituted β in ethyl acetate provides a rate acceleration of but *ca.* tenfold.¹² If (4) were in operation, the second-order rate constant would be $\sim 10^4$ greater than k_{OH} for III, a factor 10^3 greater than for an electrostatic effect β to the ester bond and 10^2 greater than an electrostatic effect α to the ester bond.¹³ That intramolecular attack is apparently

(10) *Cf.*, for example, B. M. Anderson, E. H. Cordes, and W. P. Jenks, *J. Biol. Chem.*, **236**, 455 (1961).

(11) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

(12) G. Aksnes and J. E. Prue, *J. Chem. Soc.*, 103 (1959).

(13) R. P. Bell and F. J. Lindars, *ibid.*, 4601 (1954).

favoured over a general-base-catalyzed or B_{AC}2 mechanism is surprising on the basis of the anticipated steric strain in forming the bicyclic system and from the anticipated repulsion of substituents (from Stuart-Briegleb models). The ratio of the rate constants for the hydrolysis of III to the hydrolysis of its homolog, 4(5)-hydroxyethylimidazolyl acetate,¹⁴ is reasonable on the basis of the ratios of the rates of formation of five- and six-membered rings.^{15,16}

The deuterium solvent kinetic isotope effect for the second-order hydroxide ion dependent rate for the hydrolysis of III, $k_{\text{OH}}/k_{\text{OD}} = 3.99 \times 10^2/6.87 \times 10^2 = 0.58$, is in keeping with a "normal" B_{AC}2 ester hydrolysis. Because OD^\ominus is a better nucleophile than OH^\ominus , an isotope effect of 0.5–0.7 is usually observed.^{8,17} The value of k_{OH} for III is from 40 to 220 times greater than the value of k_{OH} for the alkaline hydrolysis of *m*- or *p*-nitrobenzyl acetates,¹⁸ and approximately equal to k_{OH} for the hydrolysis of dichloroethyl acetate⁸ (as extrapolated estimating ΔH^\ddagger to be 12 kcal. mole⁻¹ for the latter reaction). Thus, assuming an approximately constant steric effect, the imidazole ring has about the same Taft σ^* ¹⁴ as a dichloromethyl function.

The effect, then, of replacing the imino hydrogen of I by a methyl group III is to change the hydrolytic pathway. At all pH values investigated, I solvolyzes *via* alkyl-oxygen cleavage and elimination of acetate, whereas III apparently undergoes a less facile intramolecular nucleophilic catalysis at low pH and an ordinary B_{AC}2 catalysis at high pH.

A mechanism analogous to (1) (where the OH^\ominus is replaced by a general base: acetate, imidazole, and pyridine) has been shown by Bruce and Fife³ to be most consistent with the data for the general-base-catalyzed hydrolysis of I. One must now, however, distinguish between (1) and (2) for the hydrolysis of I in the absence of a general base, that is, when the only bases in solution are water and OH^\ominus . Mechanism (1) involves the abstraction of a proton from the imino-nitrogen of I in a rate-determining step. This is an E₂ type mechanism. Mechanism (2) is a pre-equilibrium formation of the imidazole anion, with a subsequent rate-determining elimination of acetate ion. The pseudo-first-order rate constants for the hydrolysis of I were measured in D₂O and H₂O at a pH = pD = 9.65, and a temperature of 30°. Mechanism (1), in the pH range employed, leads to the expression

$$v = k_r[\text{OH}^\ominus][\text{E}] = (k_r K_w/a_H)[\text{E}_T] \quad (13)$$

where $[\text{E}] \cong [\text{E}_T]$. At pH 9.65, there is only an insignificant concentration of the protonated species, EH^\oplus . Since $a_H = a_D$ (pH = pD), the ratio of the observed rate constants in H₂O and D₂O is

$$k_{\text{obsd}}^{\text{H}}/k_{\text{obsd}}^{\text{D}} = k_r^{\text{H}}K_w/k_r^{\text{D}}K_{\text{D}_2\text{O}} \quad (14)$$

If a proton transfer reaction is involved in the rate-determining step, one would expect $k_r^{\text{H}}/k_r^{\text{D}} \cong 2$. At

30°, $K_w/K_{\text{D}_2\text{O}} = 6.6$,¹⁹ so that (1) would predict $k_{\text{obsd}}^{\text{H}}/k_{\text{obsd}}^{\text{D}} \cong 13$. The value of the observed rate constant, if mechanism (2) is the hydrolytic pathway for I at pH 9.65 (where $K_1 \gg a_H$), is (15).

$$k_{\text{obsd}} = k_r K_2/a_H \quad (15)$$

Since $a_H = a_D$

$$\frac{k_{\text{obsd}}^{\text{H}}}{k_{\text{obsd}}^{\text{D}}} = \frac{k_r^{\text{H}}K_2^{\text{H}}}{k_r^{\text{D}}K_2^{\text{D}}} \quad (16)$$

To evaluate the magnitude of the observed isotope effect to be expected from (2), one must estimate $k_r^{\text{H}}/k_r^{\text{D}}$, and a value for $k_2^{\text{H}}/k_2^{\text{D}}$ must be obtained. No measurements have been made to determine the isotope effect on the second dissociation constant of imidazoles K_2 . Since I readily decomposes in water, especially so at high pH's, the $\text{p}K_2$ of imidazole itself was measured. For a limited series of imidazole bases, it has been found that $\text{p}K_2 = 0.94 \text{p}K_1 + 7.43$,²⁰ providing a $\text{p}K_2$ of 13.0²¹ for I. The spectrophotometrically determined thermodynamic $\text{p}K_2$ for imidazole is 14.52,²² so that $K_2^{\text{H}}/K_2^{\text{D}}$ for I will be approximately that for imidazole. We have determined the $\text{p}K_2$ for imidazole by the conductivity method as described by Ballinger and Long.²³

The average determined value of K_2 for imidazole is $5.15 \pm 0.07 \times 10^{-16}$ in D₂O. The ratio of $K_2^{\text{H}}/K_2^{\text{D}}$ is 4.8. This falls well below a LaMer plot,²⁴ and does not agree with the empirical equation of Li,²⁵ which on the basis of a LaMer plot for the $\text{p}K_1$'s of a series of imidazoles would predict a value of 7.1 for $K_2^{\text{H}}/K_2^{\text{D}}$.

To evaluate (16) one must also assume a value for $k_r^{\text{H}}/k_r^{\text{D}}$. In the absence of any gross solvent effects, one might reasonably assume that the elimination of acetate ion from Ia would be independent of the isotopic substitution of the solvent, so that $k_r^{\text{H}}/k_r^{\text{D}} = 1$. Substitution into (16), one then predicts on the basis of (2), an observed isotope effect $k_{\text{obsd}}^{\text{H}}/k_{\text{obsd}}^{\text{D}} = 1.0 \times 4.8 = 4.8$. The observed rate constants in H₂O and D₂O were 2.08×10^{-1} and 7.77×10^{-2} min.⁻¹, respectively. An experimental value of $k_{\text{obsd}}^{\text{H}}/k_{\text{obsd}}^{\text{D}} = 2.7$ is much more in agreement with (2) (as opposed to a predicted $k_{\text{obsd}}^{\text{H}}/k_{\text{obsd}}^{\text{D}} \cong 13$ on the basis of (1)).

Since I hydrolyzes so very rapidly, it is of interest to know whether mechanism (2) is a general mechanism for all leaving groups, or whether 4(5)-X-methylimidazole hydrolyzes *via* a different mechanism when X is a good leaving group. In an approach to this question, the hydrolysis of 4(5)-chloromethylimidazole hydrochloride (V) was studied. Pyman,²⁶ who first synthesized the compound, noticed its unusual reactivity. He found that an aqueous solution of V, upon the addition of sodium carbonate, became turbid and deposited a yellow oil. When KCN was added to an alcoholic solution of V, there was no reaction. It was only after long periods of time that traces of ethyl methyl(4(5)-imidazolyl) ether were isolated. If, however, an alcoholic solution

(19) T. C. Bruce and J. J. Bruno, *J. Am. Chem. Soc.*, **83**, 3494 (1961).

(20) T. C. Bruce and G. L. Schmir, *ibid.*, **80**, 148 (1958).

(21) Using the heat of ionization for I used by Bruce and Fife,³ a value of 6.0 was calculated for $\text{p}K_1$ at 30°.

(22) H. Walba and R. W. Isensee, *J. Org. Chem.*, **21**, 702 (1956).

(23) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **81**, 1050 (1959).

(24) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 188.

(25) N. C. Li, P. Tang, and R. Mathur, *J. Phys. Chem.*, **65**, 1074 (1961).

(26) P. L. Pyman, *J. Chem. Soc.*, **99**, 668 (1911).

(14) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 3120 (1952).

(15) T. C. Bruce and U. K. Pandit, *ibid.*, **82**, 5858 (1960); see Table V.

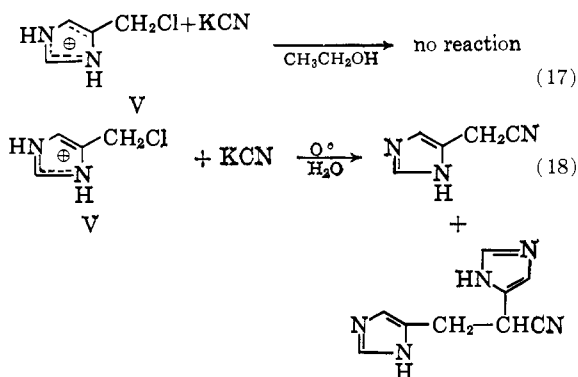
(16) T. C. Bruce and S. J. Benkovic, *ibid.*, **85**, 1 (1963).

(17) F. A. Long, *Ann N. Y. Acad. Sci.*, **84**, 596 (1960).

(18) E. Tomilla and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

The rate constants were extrapolated to 78° from data at 15, 25, and 40°. The data for the *m*-nitro ester gave rise to two possible results and the mean value is given.

of V was added dropwise to a saturated aqueous solution of KCN at 0°, a good yield of 4(5)-cyano-methylimidazole was isolated along with a small amount of 1,2-di-(4(5)-imidazolyl)propionitrile (18). Turner²⁷ found that V rapidly hydrolyzed in aqueous solution at room temperature to form 4(5)-hydroxymethyl-



imidazole. Although no kinetic measurements were made, he found that 0.1 g. of V was completely hydrolyzed after 15 min. One can easily hydrogenate V to 4(5)-methylimidazole, and the reaction of V with amines is quite exothermic.

The kinetics of the hydrolysis of V were studied at 30° and the ionic strength was kept at 1.0 by the use of KCl. The solvolysis was so facile, however, that the reaction kinetics could not be followed (by using the pH-stat) at pH values greater than 3.75. A plot of k_{obsd} , the pseudo-first-order rate constant for the hydrolysis of V, vs. pH is shown in Fig. 3. The reaction exhibits apparent first-order hydroxide ion dependence (as indicated by the slope of 1.0 for the pH-log k_{obsd} plot) so that the kinetically equivalent mechanisms of type (1) or (2) may be ruled out. Thus, if a mechanism similar to (2) were operative, the rate equation for a specific-base-catalyzed hydrolysis, as in the case of I, would have the form of (19).

$$v = \left[\frac{k_r K_1 K_2}{K_1 K_2 + K_1 a_H + a_H^2} \right] [S_T] \quad (19)$$

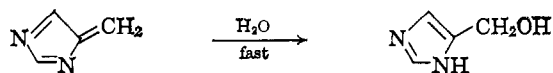
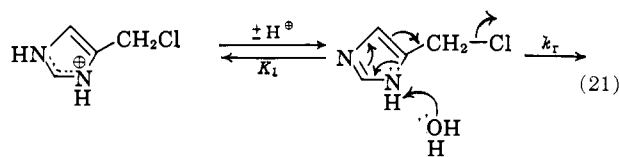
In the pH range studied, $a_H^2 \gg (K_1 K_2 + K_1 a_H)$, so that

$$k_{\text{obsd}} = k_r K_1 K_2 / a_H^2 \quad (20)$$

A plot of log k_{obsd} vs. pH should, if the reaction followed (20), have a slope of 2.0. Since the line of Fig. 3 has a slope of 1.0, specific base catalysis need not be considered as a possible mechanism. Since the kinetic measurement was made under conditions where $a_H \gg K_1$ the apparent first-order dependence of k_{obsd} on OH^- is ascribed to the ionization of V to its conjugate base and the spontaneous solvolysis of this species. By analogy to mechanism (1), one might expect water to act as a general base, in an E₂ type elimination (21).

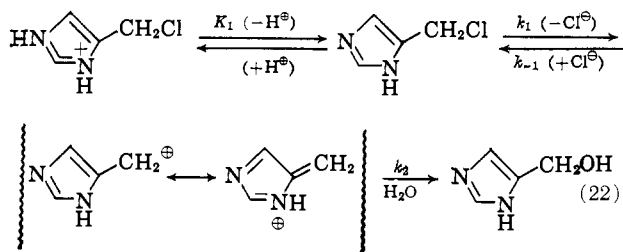
Since the imidazole nucleus possesses aromatic character one might alternatively anticipate the hydrolysis of the conjugate base of V to be similar to the hydrolysis of benzyl chlorides (*i.e.*, via a carbonium ion, a mechanism also consistent with the observed kinetics (22)).

(27) R. A. Turner, C. F. Huchner, and C. R. Scholz, *J. Am. Chem. Soc.*, **71**, 2801 (1949).



$$v = k_r \left(\frac{K_1}{K_1 + a_H} \right) [\text{H}_2\text{O}] [S_T]$$

$$k_{\text{obsd}} = \frac{k_r' K_1}{a_H} = \frac{k_r' K_1}{K_w} (\text{OH}^-) = k_{\text{OH}} (\text{OH}^-)$$



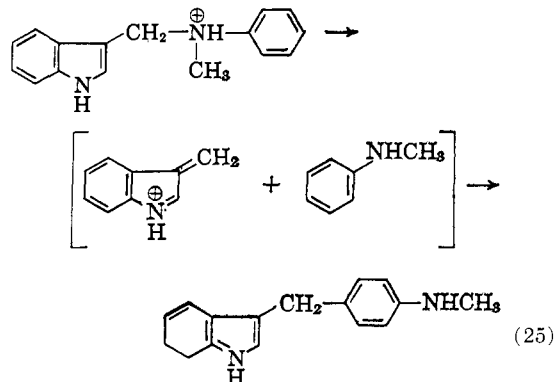
Assuming a low steady-state concentration for the carbonium ion (VI), one may derive the expression

$$k_{\text{obsd}} = \left[\frac{k_1 k_2}{k_{-1} [\text{Cl}^-] + k_2} \right] \left[\frac{K_1}{K_1 + a_H} \right] \quad (23)$$

where $[\text{Cl}^-]$ is the concentration of chloride ion in solution. If the chloride ion concentration is kept constant, and the pseudo-first-order rate constants are measured in a pH range where $a_H \gg K_1$, (23) reduces to (24). It is of interest to note that VI, the carbonium

$$v = \frac{k_r K_1}{a_H} = \frac{k_r K_1 K_w}{K_w a_H} = k_{\text{OH}} [\text{OH}] \quad (24)$$

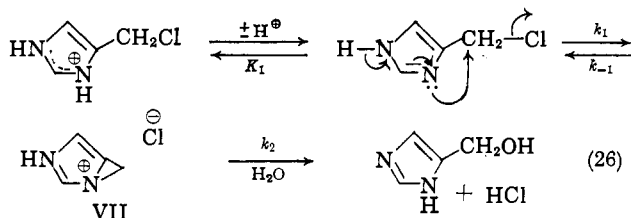
ion generated in the hydrolysis of the conjugate base of V, is the conjugate acid of the diazofulvene intermediate II. Structure VI is analogous to the intermediate proposed for the rearrangement of phenyl-3-methylindolylammonium salts²⁸ (25).



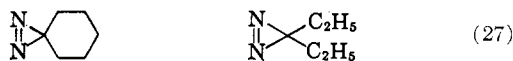
One might also think of V as the conjugate acid of a nitrogen mustard, a class of compounds which are very hydrolytically labile. Mechanism (26) is similar to the mechanism by which mustards hydrolyze.²⁹ Al-

(28) J. H. Thiesing and H. Meyer, *Ber.*, **87**, 1084 (1954).

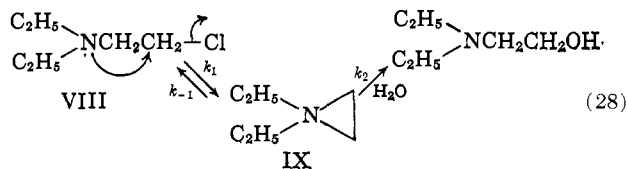
(29) (a) B. Cohen, E. R. Van Artsdalen, and J. Harris, *J. Am. Chem. Soc.*, **70**, 281 (1948); (b) P. D. Bartlett, S. D. Ross, and C. G. Swain, *ibid.*, **69**, 2971 (1947); (c) P. D. Bartlett, J. W. David, S. D. Ross, and C. G. Swain, *ibid.*, **69**, 2977 (1947).



though intermediate VII would appear to be very highly strained, one cannot *a priori* rule out such structures as unstable. The diazirines³⁰ have a ring system which is just as strained. Much work has been



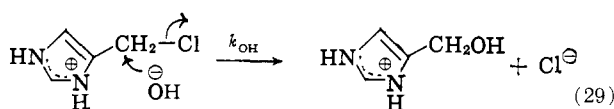
done on the kinetics of the hydrolysis of tertiary nitrogen mustards.²⁹ The compounds cyclize in a relatively fast step, followed by a much slower hydrolysis (28). For example, the rate of cyclization for bisdiethyl- β -chloroethylamine (VIII) in H₂O is 1.1 min.⁻¹ at 30°.



In 1:3 acetone-water, k_1 and k_2 for the hydrolysis of ethylbis- β -chloroethylamine are 0.24 and 0.0017 min.⁻¹, respectively.

Since the hydrolysis of V was followed by the rate of formation of HCl, if mechanism (26) is operative, the measured rate constant is that for the formation of the cyclic intermediate VII. The magnitude of the rate constant for the hydrolysis of V, when compared to the rate constants for the cyclization of mustards, is much too great to be explained in terms of (26). The value of k_1 for the conjugate base of V calculated on the basis of (26) is $\cong 2 \times 10^3$ min.⁻¹, while the rate of cyclization of VIII, which forms a much less strained ring intermediate (IX), is 1.1 min.⁻¹. Cyclization, therefore, would appear to be a very unlikely pathway for the hydrolysis. The products from the hydrolysis of V were analyzed by paper chromatography, and the results showed unequivocally that V hydrolyzes to give pure 4(5)-hydroxymethylimidazole. Secondary nitrogen mustards usually produce some dimeric materials under hydrolytic conditions^{29b} so that product analysis also points to the improbability of (26).

Direct displacement of chloride ion by hydroxide (29) in an S_N2 reaction on V is also consistent with the kinetics. The rate constant, k_{OH} , calculated on the basis of (29), is 2.8×10^{10} l. mole⁻¹ min.⁻¹, a number exceeding that for a diffusion-controlled process.

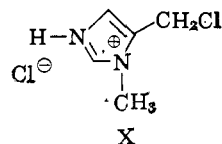


$$v = k_{OH}[\text{OH}^\ominus][\text{S}_T]$$

$$k_{\text{obsd}} = k_{OH}[\text{OH}^\ominus]$$

(30) Cf., for example, "Advances in Heterocyclic Chemistry," Vol. 2, Academic Press, Inc., New York, N. Y., 1963, p. 125.

One is left, therefore, with a choice between (21) and (22) as the mechanism for the hydrolysis of the conjugate base of V. If mechanism (21) is operative, substituting the 1-position of V should change both the mechanism and the magnitude of the hydrolytic rate constant. If, on the other hand, a carbonium ion is formed (22), the rate of hydrolysis for the N-H and the N-substituted compounds should be of approximately the same order of magnitude. 1-Methyl-5-chloromethylimidazole hydrochloride (X) was synthesized, and its kinetics of hydrolysis were measured



at 30° and pH 3.35. The value of the observed pseudo-first-order rate coefficient determined for two runs was $6.01 \pm 0.61 \times 10^{-1}$ min.⁻¹. At pH 3.35, V has an observed rate constant for solvolysis of 9.70×10^{-1} min.⁻¹.

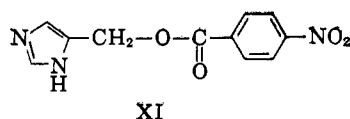
$$\frac{k_r^X}{k_r^V} = \frac{k_{\text{obsd}}^X K_1^V}{k_{\text{obsd}}^V K_1^X} = 0.620 \frac{K_1^V}{K_1^X} \quad (30)$$

One can reasonably assume that the ratio of K_1^V to K_1^X should be the same as the ratio of K_1 for imidazole to K_1 for N-methylimidazole—approximately 2.0.³¹ Thus $k_r^X/k_r^V = 1.2$, or within experimental error, as predicted by mechanism (22), the rate constants are the same. The fact that V and X hydrolyze at the same rate is additional evidence that V does not hydrolyze *via* (26), since one would expect the rate of intramolecular attack for a tertiary compound (X) to be different from that of a secondary compound.

One can also use a D₂O solvent isotope effect as a diagnostic test to distinguish between (21) and (22). In Fig. 3 there is plotted the log of the observed pseudo-first-order rate constants for the hydrolysis of V in D₂O vs. pD. As can be seen from (24), a plot of k_{obsd} vs. K_w/a_H should give a straight line of slope $k_r K_1/K_w$. Let us call this slope X. By solving for k_r and dividing we get

$$\frac{k_r^H}{k_r^D} = \frac{X^H K_w K_1^D}{X^D K_{D_2O} K_1^H} \quad (31)$$

A plot of k_{obsd} vs. K_w/a_H in H₂O and in D₂O may be found in Fig. 3. The values of X^H and X^D are 3.1×10^{10} and 6.1×10^{10} , respectively. Unfortunately, K_1 for V cannot be determined; however, if one allows the assumption that the electronic effect on the pK_1 of V of a side chain chloride group is the same as that of a *p*-nitrobenzoyl group, then the pK_1 of V would be the same as that for 4(5)-hydroxymethylimidazolyl *p*-nitrobenzoate (XI).



pK_1 of XI was found to be 5.61. Using this value, a LaMer type plot²⁵ gives a value for K_1^D/K_1^H of 0.38. For the first dissociation constant, (K_1) for imidazoles,

(31) K. Hofmann, "Imidazole and its Derivatives, Part I," Interscience Publishers, Inc., New York, N. Y., 1953, p. 15.

a LaMer type plot is applicable.²⁵ Substituting these numbers into eq. 31 gives a value of $k_r^H/k_r^D = 1.25$. Fortuitously, the deuterium solvent kinetic isotope effect for the hydrolysis of *t*-butyl chloride, which solvolyzes *via* a carbonium ion, is 1.25.³²

The rate of hydrolysis of V, if the reaction does indeed proceed *via* a carbonium ion, should be sensitive to the concentration of chloride ion in solution (see 23) and one should be able to observe a "mass law" effect.

$$k_{\text{obsd}} = \frac{k_{\text{obsd}}^{\circ} k_2}{k_{-1}[\text{Cl}^{\ominus}] + k_2} \quad \text{or} \quad \frac{1}{k_{\text{obsd}}^x} = \frac{k_{-1}[\text{Cl}^{\ominus}]}{k_{\text{obsd}}^{\circ} k_2} + \frac{1}{k_{\text{obsd}}^{\circ}} \quad (32)$$

where k_{obsd}^x is the observed pseudo-first-order rate constant at any chloride ion concentration (x) and k_{obsd}° is the pseudo-first-order rate constant when $[\text{Cl}^{\ominus}] = 0$. A plot, therefore, of $1/k_{\text{obsd}}^x$ vs. $[\text{Cl}^{\ominus}]$ should give a straight line of slope $k_{-1}/(k_{\text{obsd}}^{\circ} k_2)$ and an intercept of $1/k_{\text{obsd}}^{\circ}$. Such a plot is found in Fig. 4. The hydrolysis was carried out at various concentrations of LiCl with LiClO₄ added to keep the ionic strength at 1.0. Both the salt bridge and the calomel electrode contained saturated solutions of LiCl. From the slope of Fig. 4, which is 1.85, and from a knowledge of k_{obsd}° , one calculates that $k_{-1}/k_2 = 3.86$. Since $k_1 = k_{\text{obsd}}^{\circ} a_H/K_1$, an assumed pK_1 of 5.6 for V leads to $k_1 \cong 2 \times 10^3 \text{ min.}^{-1}$.

One might inquire as to how a rate constant of $2 \times 10^3 \text{ min.}^{-1}$ for the hydrolysis of V compares to the rate of solvolysis of other compounds which undergo carbonium ion formation. The α -halo ethers solvolyze in water to form carbonium ions at a rate which probably exceeds the corresponding rate for any other group of compounds reported to date. Perhaps the most hydrolytically labile α -halo ether is chloromethyl ethyl ether (XII)³³ which has a first-order hydrolytic rate constant of 0.14 min.^{-1} in 2% water-dioxane. Attempts were made in our laboratories to measure the rate of hydrolysis of chloromethyl methyl ether in pure water, but the reaction was over before mixing was completed. Böhme³³ also reported the rate of hydrolysis of chloromethyl phenyl ether (XIII), and its variation with water concentration in dioxane-water solvent mixtures. If one takes Böhme's data for the hydrolysis of XIII, and plots $\log k_{\text{obsd}}$ vs. the mole fraction of water in the solvent, a smooth line is obtained. At a mole fraction of 0.35, which was the highest concentration of water employed, the line already begins to flatten out owing to selective solvation. The data could therefore be extrapolated to 100% if one assumes the continuing form of the curve to give an answer correct within an order of magnitude. The data for the hydrolysis of the ethyl ether XII (in 2% aqueous dioxane) was fitted to the function describing the solvent sensitivity for the phenyl ether XIII. An extrapolated rate constant of $\sim 4 \times 10^2 \text{ min.}^{-1}$ is obtained for the hydrolysis of XII in 100% H₂O. Both XII and XIII should have approximately the same solvent sensitivity, since their transition states are probably very similar. It would appear, therefore, that X hydrolyzes to form a carbonium ion at least as fast (if not faster) than any other compound whose solvolysis has been studied.

(32) P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **34**, 1714 (1956).

(33) H. Böhme and A. Corries, *Ber.*, **89**, 719 (1956).

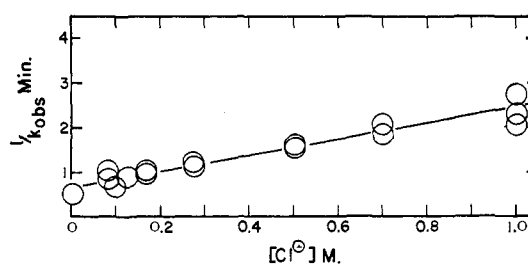


Fig. 4.—Plot of the reciprocal of the determined pseudo-first-order rate constants determined at constant pH vs. the reciprocal of the chloride ion concentration (30°, solvent water, $\mu = 1.0 \text{ M}$ with LiClO₄).

Experimental

4(5)-Hydroxymethylimidazole hydrochloride,³⁴ 4(5)-chloromethylimidazole hydrochloride (V),³⁵ 4(5)-hydroxymethylimidazolyl acetate (I),³ and 1-methyl-5-chloromethylimidazole hydrochloride (X)³⁶ were synthesized by literature procedures. Freshly recrystallized *p*-nitrophenyl acetate was the same as from previous studies.¹⁶ Melting points were determined on a Nalge electric melting point block, and are uncorrected. 1-Methyl-5-hydroxymethylimidazole was synthesized by the method of Jones³⁶; however, a crucial step in the methanolysis of sarcosinonitrile was omitted in the experimental procedure, so that the full preparation of the methyl ester of sarcosine is reported herein. The remainder of the preparation proceeds smoothly as described.

A mixture of 135 g. (2.0 moles) of methylamine hydrochloride, 270 ml. of 37% formaldehyde, and 100 ml. of water were stirred in a round-bottom flask at 0° for 3 hr. A cold concentrated solution of 130 g. (2.0 moles) of potassium cyanide was added in portions over a period of 2 hr., the temperature not being allowed to rise above 8°. Solid CO₂ was added from time to time to ensure a CO₂ atmosphere. The mixture was stirred for 1 additional hour, and was then extracted with two 500-ml. portions of ether. After drying the ethereal solution over calcium oxide, the ether was removed by flash evaporation. The crude sarcosinonitrile was dissolved in 2.5 l. of dry methanol previously saturated in the cold with HCl. The solution was allowed to stand overnight at room temperature and was then heated under reflux for 4.5 hr. The ammonium chloride which had precipitated was removed by filtration, and the filtrate was flash evaporated to a volume of 800 ml. The solution was once again filtered through a pad of Filter-cell, and the filtrate was evaporated to dryness. The residue was dissolved in 100 ml. of water, and the water was removed under vacuum. Formylation was then carried out as described.³⁶

1-Methyl-5-hydroxymethylimidazolyl Acetate (III) Hydrochloride.—To 0.50 g. of 1-methyl-5-hydroxymethylimidazole (0.0045 mole) was added 6.0 ml. of acetyl chloride. The mixture was stirred magnetically under reflux for 2 hr., after which time an additional 2.5 ml. of acetyl chloride was added and refluxing was continued for 1 more hr. The material was cooled and poured into about 350 ml. of anhydrous ether. The precipitate was filtered and washed with ether until the odor of acetyl chloride could no longer be detected. The ester hydrochloride was dissolved in the minimum amount of absolute alcohol, anhydrous ether was carefully layered over the solution, and the mixture was refrigerated overnight. The resulting crystals were filtered and the procedure was repeated until a constant melting point was obtained. The final product was dried *in vacuo* over P₂O₅; yield 0.48 g. (55%) of III, m.p. 130–131°.

Anal. Calcd. for C₇H₁₁N₂O₂Cl: N, 14.70; Cl, 18.60. Found: N, 14.42; Cl, 18.32.

1-Methyl-5-hydroxymethylimidazolyl Succinate (IV).—1-Methyl-5-hydroxymethylimidazole (1.0 g., 0.009 mole) was added to a suspension of 1.0 g. (0.01 mole) of succinic anhydride in 10 ml. of dry xylene. The mixture was stirred magnetically under reflux for 5 hr., the reaction mixture was cooled, and the product collected by filtration. The precipitate was repeatedly washed with boiling xylene to remove the unreacted anhydride; 1.78 g. (94%) of 1-methyl-5-hydroxymethylimidazolyl succinate

(34) J. R. Totler and W. J. Darby, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 460.

(35) R. G. Jones and K. C. McLaughlin, *J. Am. Chem. Soc.*, **71**, 2444 (1949).

(36) R. G. Jones, *ibid.*, **71**, 644 (1949).

was obtained, m.p. 149–155° (dec.) The compound was recrystallized twice from ethanol-acetonitrile and dried *in vacuo* over P₂O₅. In this manner 0.78 g. of analytically pure material was obtained, m.p. 169–171° (decomposed compound was put into melting block at 140°).

Anal. Calcd. for C₆H₁₂O₄N₂: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.90; H, 5.68; N, 13.02.

Sodium Monomethyl Succinate.—Monomethyl succinate was prepared from the alcohol and succinic anhydride³⁷; 0.58 g. of the ester was dissolved in 30 ml. of methanol in which was suspended 1.16 g. of an ion exchange resin (Bio-rex 70, Cal-Biochem, 100–200 mesh, sodium form). After 20 min., the suspension was filtered and a large excess of anhydrous ether was added to the filtrate. The precipitated salt was filtered and washed with ether; 0.49 g. of the sodium salt was obtained (71%).

4(5)-Hydroxymethylimidazolyl *p*-Nitrobenzoate (XI).—To 0.2 g. (0.002 mole) of 4(5)-hydroxymethylimidazole suspended in 35 ml. of hot ethyl acetate was added a solution of 0.55 g. (0.003 mole) of freshly recrystallized *p*-nitrobenzoyl chloride in 5 ml. of ethyl acetate. The solution was refluxed for 75 min. The resulting suspension was filtered, and the ester hydrochloride was washed with benzene and then with ether; 0.48 g. (94%) of a compound melting at 164–166° was obtained; after repeated recrystallization from absolute alcohol and alcohol-acetonitrile mixtures, the melting point was 186–187.5°.

Anal. Calcd. for C₁₁H₁₀O₄N₂Cl: C, 46.57; H, 3.55; N, 14.81; Cl, 12.50. Found: C, 46.21; H, 3.72; N, 15.09; Cl, 12.38.

Reaction of IV with Sodium Methoxide in Methanol.—To a solution of 0.102 g. (0.00189 mole) of sodium methoxide (Matheson Coleman and Bell) in 10 ml. of anhydrous methanol was added 0.20 g. (0.000943 mole) of 1-methyl-5-hydroxymethylimidazolyl succinate (IV). The solution was stirred in a nitrogen atmosphere at room temperature for 3 hr. Anhydrous ether was added to the solution until no more precipitate was seen to form. The precipitate was filtered, washed with anhydrous ether, and dried over P₂O₅ under vacuum oven at 50°. The yield was 0.0682 g. (47%) of a compound whose infrared spectrum was identical with that of an authentic sample of sodium monomethyl succinate.

Reaction of III with Hydroxylamine.—To determine the extent of reaction of III with hydroxylamine, the reaction of *p*-nitrophenyl acetate (*p*-NPA) with hydroxylamine was used as a reference. It was assumed that *p*-NPA reacted to provide a quantitative yield of acethydroxamic acid. The standard solutions have been described previously³⁸ and a reaction time of 45 min. at 65° was employed. The extent of reaction to form acethydroxamic acid as determined from a Beer's line employing *p*-NPA as standard was 92.5%.

Product Analysis for the Hydrolysis of V.—A small amount (ca. 0.01 g.) of 4(5)-chloromethylimidazole (as the hydrochloride V) was dissolved in ~5 ml. of water, and let stand at room temperature for 2 hr. Varying amounts of the solution were spotted on Whatman No. 1 paper and paper chromatographed for 12 hr. in both 3:1 propanol-1 *N* acetic acid and 3:1 propanol-0.2 *N* NH₃. The chromatograms were developed with Pauli coupling reagent as described by Ames and Mitchell.³⁹ Only one spot was found for any of the chromatograms. This spot had the same *R_f* value as an authentic sample of 4(5)-hydroxymethylimidazole employed as a control. Some chromatograms were developed with ninhydrin spray to detect any amines which might result from ring cleavage, but no other product but 4(5)-hydroxymethylimidazole could be found.

Kinetics.—All the rate constants reported herein were determined on a Radiometer TTT 1b pH-stat assembly as previously described.³ Constant temperature, ±0.1°, in the micro-titration cell was obtained with a Haake circulating bath. The sample solution (ca. 2 ml.) was titrated with ~0.01 *N* KOH ($\mu = 1.00$ with KCl) delivered through an Alga trubore syringe. The pseudo-first-order rate constants were calculated by the method of Guggenheim,⁴⁰ and some data was spot checked by plotting $\log(\alpha/(a-x))$ against time.

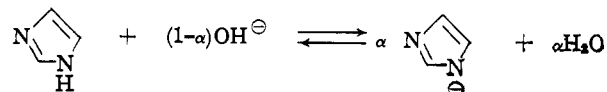
(37) W. A. Bone, J. J. Sudborough, and C. H. G. Sprankling, *J. Chem. Soc.*, **85**, 535 (1904).

(38) T. C. Bruce and F. H. Marquart, *J. Am. Chem. Soc.*, **84**, 365 (1962).

(39) B. N. Ames and H. K. Mitchell, *ibid.*, **74**, 252 (1952).

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

***pK₂* of Imidazole.**—The *pK₂* of imidazole in H₂O and 99.5% D₂O was measured conductometrically by the method of Ballinger and Long.²³ When imidazole is dissolved in dilute NaOH, the following equilibrium is established



$$K = \frac{\alpha}{(1-\alpha)(\text{ImH})} = \frac{K_2}{K_w} \quad (33)$$

The resistance (corrected for viscosity), *R_c*, of an imidazole solution in dilute NaOH is related to the resistance of a solution of the same concentration of NaOH in the absence of imidazole, *R₀*, in the following way

$$\frac{R_0}{R_c} = \frac{\Delta_c \text{NaOH}}{\lambda_c \text{Na}^{\oplus} + (1-\alpha)\lambda_c \text{OH}^{\ominus} + \alpha\lambda_c \text{Im}^{\ominus}} \quad (34)$$

where $\lambda_c \text{Na}^{\oplus}$, $\lambda_c \text{OH}^{\ominus}$, and $\lambda_c \text{Im}^{\ominus}$ are the ionic mobilities of the ions at their respective concentrations. The equivalent conductance of the alkaline solvent at concentration *C* is $\Delta_c \text{NaOH}$. Both in H₂O and D₂O, the ionic mobility of the imidazole anion, $\lambda_c \text{Im}^{\ominus}$, was determined graphically.²⁰ The values are 28.8 and 23.6 mhos, respectively. The ratio of the ionic mobilities in H₂O and D₂O, as might be expected from a consideration of Stoke's law, was the inverse ratio of the viscosities of the solvents. Solving (34) for α and substituting into (33), *K* may be calculated. Thus, from a knowledge of *K_w*, *K₂* may be obtained. Because of its high *pK₂*, concentrated solutions of imidazole were employed so that it was necessary to make viscosity corrections. The corrected resistance $R_c = R_1(\eta_0/\eta_1)$, where *R₁* is the measured resistance and η_0/η_1 is the ratio of the viscosity of the alkaline solvent to that of the imidazole solution.

Conductivity measurements were made on the apparatus described by Ballinger and Long.²³ The cell constant for the conductivity cell was 1.86155 cm.⁻¹. Viscosities were determined using a Cannon-Fenske type viscometer, and the data obtained were reproducible to better than 0.2%. The temperature was kept at 25.0 ± 0.01° for all measurements.

Imidazole (Eastman Kodak White label) was recrystallized twice from a mixture of acetone-petroleum ether (60–90°), and was dried *in vacuo* over a mixture of P₂O₅ and paraffin wax. Standard stock solutions of NaOH and NaOD in H₂O and D₂O were made up. The imidazole was weighed into a dry 50-ml. volumetric flask and 10.0 ml. of the stock NaOH solution was added. The imidazole was brought into solution and H₂O (or D₂O) was added to the mark. Only CO₂-free deionized H₂O was used, and the D₂O employed was boiled to exclude CO₂. Conductivity measurements were made on these solutions directly; however, the solutions were filtered free of any dust particles before viscosities were determined (Table I). The average value of *K₂* for imidazole is 2.48 ± 0.01 × 10⁻¹⁶ in H₂O and 5.15 ± 0.07 × 10⁻¹⁶ in D₂O.

TABLE I

Imidazole, <i>M</i>	<i>R</i> , ohms	η_0/η	<i>R_{cor}</i>	<i>K₂</i> × 10 ⁻¹⁶
Solvent: 0.03008 <i>M</i> NaOH in H ₂ O				
0	262.61	1.0000	262.6	
1.006	332.24	0.9084	301.8	2.47
0.6583	308.45	.9353	288.5	2.48
.3555	287.04	.9656	277.2	2.48
.2090	277.41	.9777	271.2	2.47
Solvent: 0.01013 <i>M</i> NaOD in ca. 99.5% D ₂ O				
0	1198.6	1.0000	1199	
0.9739	1540.9	0.9065	1397	4.99
.7283	1462.6	.9282	1358	5.24
.2996	1308.0	.9691	1308	5.22

Acknowledgment.—This work was supported by grants from the National Institutes of Health and the National Science Foundation.