panol-1-*t* with ordinary Lucas reagent were converted into the corresponding Grignard reagents. Each sample was cooled in an ice bath while oxygen was bubbled into the reaction mixture for 1 hr. The resulting material was decomposed by the addition of dilute HCl and then subjected to continuous extraction with ether for 24 hr. After drying and the removal of most of the ether, the residue was purified by preparative vpc[4] to give pure 1-propanol. When necessary, inactive 1-propanol was added as carrier before it was degraded by oxidization to propionic acid and then acetic acid as previously described.[4] In preliminary trials using inactive materials, the conversion of 1-chloropropane to 1-propanol was found to proceed in yields of 50–60%.

Kinetics of Proton Transfer from the α Carbon of Ethyl Thioacetate and Its Dimethyliminium Derivative[1]

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Abstract: Rate constants at 25° for the hydrolysis of and enamine formation from ethyl N,N-dimethylthioacetimidate, $CH_3C(=N^+(CH_3)_2)SC_2H_5$, have been determined. Both reactions are catalyzed by general bases; enamine formation occurs more rapidly than hydrolysis. The rate constant for abstraction of a proton by hydroxide ion from the α carbon of ethyl thioacetate at 25° has also been determined. Comparison of this rate constant with that for the analogous reaction of ethyl N,N-dimethylthioacetimidate shows that $C(=N^+(CH_3)_2)SR$ activates an α-hydrogen atom for proton transfer to hydroxide ion about 2×10^4 times better than C(=O)SR.

The kinetic acidity of the α-hydrogen atoms of simple thiol esters has not previously been determined. In this paper we describe the determination of the rate constant for the abstraction by hydroxide ion of an α-hydrogen atom from ethyl thioacetate, based upon a method of tritium–hydrogen exchange. In addition, in order to compare the effect of the dimethyliminium function with the carbonyl function, we have measured the rates of base-catalyzed enamine formation from ethyl N,N-dimethylthioacetimidate ($CH_3C(=N^+(CH_3)_2$-SC_2H_5) and also determined the kinetics of hydrolysis of this compound. In the Discussion we consider the relevance of our results to the mechanisms of enzymatic reactions which involve reaction at the α carbon of thiol esters.

Experimental Section

Materials. Ethyl thioacetate was purchased from J. T. Baker Chemical Co. and redistilled before use. 1,1-Cyclobutanedicarboxylic acid was recrystallized from ethyl acetate–1,2-dichloroethane (1:3).

Ethyl N,N-dimethylthioacetimidate bromide was prepared by the reaction of N,N-dimethylthioacetamide with ethyl bromide.[2] In a typical preparation, N,N-dimethylthioacetamide (3.5 g) was refluxed with ethyl bromide (11 ml) in dry acetone (12 ml) for 21 hr, with stirring. Enough anhydrous ether was then added to precipitate completely the product, which was collected, washed thoroughly with anhydrous ether, and dried and stored over phosphorus pentoxide in an evacuated desiccator; 5.2 g (74% of theory) of a white crystalline deliquescent solid, mp 139–141° (with gas evolution), was obtained. *Anal.* Calcd for $C_6H_{14}BrNS$: C, 33.97; H, 6.65; Br, 37.66; N, 6.60. Found: C, 33.74; H, 6.65; Br, 37.73; N, 6.63. The ultraviolet spectrum of a freshly prepared solution in 10^{-2} *N* HCl, taken before the thioacetimidate had undergone more than 1% hydrolysis, showed λ_{max} 254 mμ (ε 11,000). This spectrum is similar to that reported[3] for protonated thioacetimidic acid ethyl ester in water (λ_{max} 243 mμ (ε 9950)). The proton magnetic resonance (pmr) spectrum of a freshly prepared 0.2 *M* solution in 10^{-4} *N* DCl in D_2O had signals at δ 1.39 (triplet, *J* = 7.5 Hz, 3 H, CH_3CH_2), 2.66 (singlet, 3 H, $CH_3C(=N)S$), 3.31 (quartet, *J* = 7.5 Hz, 2 H, CH_3CH_2S), and 3.48 and 3.55 (two singlets, 6 H, $N(CH_3)_2$). This and all other pmr spectra were taken on a Varian A-60 spectrometer operating at 60.00 MHz. Chemical shifts (δ in parts per million) are relative to the external standard of tetramethylsilane in chloroform.

Kinetic Measurements. The rates of hydrolysis of ethyl N,N-dimethylthioacetimidate in hydrochloric acid, potassium acetate, potassium 1,1-cyclobutanedicarboxylate, and potassium phosphate buffers were followed spectrophotometrically at 260 mμ. Each reaction was initiated by the addition of a small volume (0.5 ml or less) of a freshly prepared concentrated solution of the iminium compound in 10^{-4} *N* HCl to 80 ml of a temperature-equilibrated solution of buffer and potassium chloride (a sufficient amount to give an ionic strength of 0.5 *M*) in a stoppered 100-ml volumetric flask. The reaction mixtures, which initially contained 10^{-4} *M* iminium compound, were maintained at 25.0° in a water bath. At various times a 3-ml aliquot was removed from each reaction mixture and its absorbance immediately measured at 260 mμ with a Zeiss PMQ II spectrophotometer against a blank the composition of which was identical with the reaction mixture except for the omission of the iminium compound. The hydrolyses were followed for at least two half-times, and the first-order rate constants were calculated from the resulting linear semilogarithmic plots of absorbance against time by use of the relationship $k_{obsd} = 0.69/t_{1/2}$. This procedure was altered slightly in measuring the faster rates of hydrolysis in potassium carbonate, triethylenediamine (1,4-diazabicyclo[2.2.2]octane), and imidazole buffers. In these cases reaction mixtures were contained in stoppered 3-ml, 1-cm cuvettes placed in the thermostated cell holder of the spectrophotometer. The absorbance at 270 or 253 mμ relative to water in the blank cuvette was recorded as a function of time, and the first-order rate constants were obtained from the linear semilogarithmic plots of $A_t - A_\infty$ against time, where A_t is the absorbance at time *t* and A_∞ is the final absorbance.

The rates of reaction of iodine with ethyl N,N-dimethylthioacetimidate were determined by measuring the decrease in absorbance of triiodide ion at 351 mμ.[4] The reaction mixtures contained the iminium thiol ester (5×10^{-2}–10^{-3} *M*), buffer (0.005–0.030 *M*), potassium iodide (0.005 *M*), sufficient potassium chloride to give an ionic strength of 0.5 *M* (0.43–0.48 *M*), and iodine (as I_2, I_3^-, I_2Br^-, and I_2Cl^-; initially 4×10^{-5} or 8×10^{-5} *M*). All these components except the iminium compound were prepared in

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[1] This research was supported by a grant (GB 4848) from the National Science Foundation. Address inquiries to G. E. L.

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[3] G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, 87, 3863 (1965).

[4] E. T. Harper and M. L. Bender, *ibid.*, 87, 5625 (1965).

stoppered 3-ml, 1-cm cuvettes and equilibrated at 25.0°. Reaction was initiated by the addition of an aliquot from a stock solution of the iminium compound in 10^{-4} *N* HCl. This stock solution was prepared within 4 hr of use so that less than 3% hydrolysis had occurred (see Results) and was kept at 25° with moist nitrogen bubbling through it so that any ethanethiol which formed upon hydrolysis was swept out at once. The rates of iodination were always determined in pairs: one reaction mixture contained an initial total iodine concentration of 4×10^{-5} *M*, and the other reaction mixture was identical except that it contained an initial total iodine concentration of 8×10^{-5} *M*. Under the conditions reported in this paper, the plots of absorbance against time were linear until the absorbance had decreased to 15% or less of its initial value. The independence of rate upon iodine concentration was further shown by the fact that for each pair the slopes of the plots always agreed within ±5% of the average. The observed first-order rate constants were calculated from the linear slopes of the plots of absorbance at 351 mμ against time by use of the equation k_{obsd} = slope/(26,000 × 0.70 × [ethyl N,N-dimethylthioacetimidate]). In this equation 26,000 M^{-1} cm^{-1} is the extinction coefficient of the triiodide ion at 351 mμ and 0.70 is the fraction of the total iodine concentration in the reaction mixtures that exists as triiodide ion.[4] The value of 0.70 is the ratio of the average of the absorbances that were measured at 351 mμ and 25° for 3.4×10^{-5} *M* iodine in 0.005 *M* potassium iodide–0.43 *M* potassium chloride–0.001 *M* potassium bromide (0.62) and in 0.005 *M* potassium iodide–0.48 *M* potassium chloride–0.005 *M* potassium bromide (0.61) to that measured for 3.4×10^{-5} *M* iodine in 0.5 *M* potassium iodide (0.89). In the latter solution, the iodine exists almost completely as triiodide ion ($K = [I_3^-]/[I_2][I^-] = 660\ M^{-1}$ [4]) whereas in the first two solutions, which encompass the range of concentrations of halide ions present in the reaction mixtures, the iodine exists as free iodine, triiodide ion, iodine chloride ion ($K = [I_2Cl^-]/[I_2][Cl] = 1.7\ M^{-1}$ [5]), and very slightly as iodine bromide ion ($K = [I_2Br^-]/[I_2][Br^-] = 15\ M^{-1}$ [6]). This method can be used because the absorbances at 351 mμ of iodine (ϵ 20[7]), iodine chloride ion (ϵ 190 [5]), and iodine bromide ion (ϵ 3300 [6]) are sufficiently less than that of the triiodide ion that they can be neglected. For several constant conditions of pH and buffer concentration the rates of iodine disappearance were measured at more than one concentration of the iminium thiol ester; it was found that the rates were always proportional to its concentration. The rates of reacton of iodine with the possible products of hydrolysis of ethyl N,N-dimethylthioacetimidate under a range of conditions which encompassed those used in studying the reaction of the iminium compound itself with iodine were also measured spectrophotometrically by the disappearance of triiodide ion. No significant reaction occurred between iodine and 10^{-4} *M* ethyl thioacetate, N,N-dimethylacetamide, and dimethylammonium ion. Ethanethiol at concentrations of 10^{-4} *M* to 2×10^{-5} *M* reacted rapidly (complete within 30 sec) with iodine. The stoichiometry of the reaction (2 mol of ethanethiol/mol of iodine) indicated oxidation to the disulfide.

Measurements of the pH values of the reaction mixtures from the kinetic studies of hydrolysis and iodination were made at the end of the reactions with a Radiometer 25 SE pH meter.

The rates of alkaline hydrolysis of ethyl thioacetate were measured by following the decrease in absorbance of the thiol ester at 235 mμ.[8] The reaction mixtures, which were maintained at 25.0° in a water bath, contained ethyl thioacetate (initially 5×10^{-4} *M*), sodium hydroxide (10^{-2} or 2×10^{-2} *N*), and sufficient sodium chloride to give an ionic strength of 0.33 *M*. Reaction was initiated by adding 1 ml of 0.01 *M* ethyl thioacetate to 19 ml of a temperature-equilibrated mixture of the other components. At various times, 0.6-ml aliquots were removed and added to 2.4 ml of 10^{-2} *N* HCl, and the absorbances of these read at 235 mμ. The semilogarithmic plots of $A_t - A_\infty$ against time were linear and yielded the observed first-order rate constants. The values which were obtained for k_{obsd} in 0.01, 0.01, and 0.02 *N* sodium hydroxide are 0.063, 0.060, and 0.106 min^{-1}, respectively. The resulting average value of 5.9 M^{-1} min^{-1} for the second-order rate constant can be compared with the value of 0.65 M^{-1} min^{-1} reported for the alkaline hydrolysis of ethyl thioacetate at 0°.[8]

Product Identification. Ethyl N,N-dimethylthioacetimidate bromide (85 mg, 0.4 mmol) was dissolved in 2 ml of 0.3 *M* $KDCO_3$–K_2CO_3 buffer, 90% carbonate, in D_2O. The hydrolysis of the iminium compound was followed by measuring the decrease in absorbance at 253 mμ of 5-μl aliquots of the reaction mixture in 10 ml of 10^{-2} *N* HCl and was complete within 60 min. The reaction mixture was then adjusted to pD 8 by the addition of 0.1 ml of 2 *N* DCl in D_2O. The pmr spectrum of the acidified reaction mixture, which was cloudy due to the partial separation of ethanethiol, showed signals at δ 2.07, 2.88, and 3.03 (all singlets), which corresponds to the pmr spectrum that was obtained for N,N-dimethylacetamide in D_2O, and signals at δ 1.28 (triplet, J = 7.5 Hz) and 2.57 (quartet, J = 7.5 Hz), which corresponds to the pmr spectrum that was obtained for ethanethiol in D_2O. The other possible pair of products from hydrolysis is ethyl thioacetate and dimethylammonium ion. The pmr spectrum of these compounds, which were taken in D_2O ($CH_3C(=O)SC_2H_5$ δ 1.17 (triplet, J = 7.5 Hz), 2.32 (singlet), and 2.83 (quartet, J = 7.5 Hz); $(CH_3)_2NH_2Cl$ 2.73 (singlet)), were completely absent in spectra of the products from the reaction mixture.

Hydrogen Isotope Incorporation. The extent of deuterium incorporation into the α position of ethyl N,N-dimethylthioacetimidate that occurred simultaneously with its hydrolysis in D_2O was determined at pD values of 9.93 and 10.20. The experiment at pD 10.20 was carried out in the following way. A freshly prepared 0.2 *M* solution of the iminium compound in 10^{-4} *N* DCl (1 ml) was added to 19.0 ml of 0.001 *M* $KDCO_3$–10^{-2} *M* KCl in a jacketed beaker thermostated at 25.0°. The pD was maintained at 10.18–10.22 by the addition of 0.15 *N* KOD in a Radiometer pH-Stat apparatus. Nitrogen was continuously bubbled through the reaction mixture in order to remove the ethanethiol which formed. The deuterium content of the reaction mixture was greater than 99.7 atom % and the calomel electrode of the pH-Stat contained a saturated solution of potassium chloride in D_2O rather than H_2O in order to prevent any dilution of the D_2O content. The pD value was obtained from the reading on the pH meter by the relationship, pD = meter pH reading + 0.4.[9] During the hydrolysis 1 equiv of base was consumed, and the observed first-order rate constant for hydrolysis was obtained from the slope of a semilogarithmic plot of the total amount of base consumed less the amount consumed at various times against time. After the hydrolysis had proceeded for ten half-times, the reaction mixture was adjusted to pD 6 by the addition of 2.7 ml of 10^{-2} *N* DCl and concentrated to a volume of 1.5 ml on the rotary evaporator at 30° or less. The pmr spectrum of the concentrate showed only the signals from N,N-dimethylacetamide and HDO. The fractional hydrogen content of the α position of the N,N-dimethylacetamide was obtained by comparison of the integrated intensity of the α-methyl group with that of the two N-methyl groups (six hydrogens). In a control experiment in which N,N-dimethylacetamide was maintained in D_2O at pD 10.2 for the same period of time and worked up in an identical way there was no incorporation of deuterium into the α position of the N,N-dimethylacetamide. The exchange experiment that was done at pD 9.93 was carried out in exactly the same way except that the initial concentration of the iminium compound was 0.02 *M* and the concentration of the carbonate buffer was 0.002 *M*.

The extent of tritium incorporation into the α position of ethyl thioacetate that occurred simultaneously with alkaline hydrolysis in tritium water was determined. In one experiment, sodium hydroxide in ^{3}H water (0.2 ml of 0.5 *N* containing about 15 mCi of ^{3}HHO) and ethyl thioacetate (0.1 ml of 0.05 *M*), both at 25°, were mixed in a 2-ml, stoppered volumetric flask and maintained at 25°. Under these conditions the half-time for hydrolysis of the thiol ester is about 0.4 min. Five microliters of the reaction mixture was removed with a micropipet and diluted with 1 *N* NaCl for the determination of the tritium content of the water. After 10 min, the reaction mixture was adjusted to about pH 7 (checked with pH paper) by the addition of 0.05 ml of 1.75 *N* HCl–0.1 *M* H_3PO_4, diluted to 2.0 ml with water, and put on a small column (12 cm × 0.2 cm^2) of Bio-Rad AG 1-X8 anion-exchange resin, chloride form. The column was washed with water until the effluent contained no counts above background. The [^{3}H] acetate was then eluted from the column with five 2-ml portions of 1 *N* sodium chloride. In a control experiment which was identical except for the substitution of sodium [^{3}H] acetate for the ethyl thioacetate it was found that 95% of the acetate was recovered in the effluent upon elution with 1 *N* NaCl, as measured by the counts per minute (cpm) of tritium introduced and recovered. Consequently, the specific activity of the acetate from the hydrolysis, expressed as cpm per microatom of

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[9] T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961), and references therein.

α hydrogen, was taken as the total cpm recovered in the 1 N NaCl effluent fractions divided by 0.95 times 3 times the total initial micromoles of ethyl thioacetate. Another determination of extent of tritium incorporation was carried out in an identical way except that the hydrolysis mixture contained 0.2 ml of 0.25 N NaOH–0.25 N NaCl in ^{3}HHO rather than 0.2 ml of 0.5 N NaOH in ^{3}HHO.

A more complete experiment was performed to make certain that the tritium eluted from the ion-exchange resin after the water wash was, in fact, in the acetate. In this case, the reaction mixture from the hydrolysis at 25° of ethyl thioacetate (10 μmol in 0.30 ml of 0.17 M NaOH in ^{3}HHO for 10 min) was adjusted to about pH 7 with 0.45 ml of 0.092 M acetic acid, diluted with water to 2 ml, and put on a small column (0.5 cm × 0.2 cm^2) of Bio-Rad AG 1-X8 200–400 mesh anion-exchange resin, acetate form. After the column had been washed with water until the ^{3}HHO had been completely washed out, the acetate from the hydrolysis was eluted with six 2-ml portions of 0.062 M S-benzylthiuronium acetate. A control experiment with [^{3}H] acetate showed that 95% of the [^{3}H] acetate applied to such a column is recovered in the elution with the S-benzylthiuronium acetate, based upon recovery of tritium. The eluted acetate from the hydrolysis was further diluted with enough 0.06 M S-benzylthiuronium acetate so that if all the tritium associated with it were in the acetate, the specific activity of the S-benzylthiuronium acetate would be 22 cpm/μmol. The solution of S-benzylthiuronium acetate was concentrated with the rotary evaporator, and the crystals of S-benzylthiuronium acetate (mp 131–132°, lit.[10] 134°) which formed were collected and dried. The specific activity of the S-benzylthiuronium acetate was 21 cpm/μmol after this first crystallization and was 23 cpm/μmol after recrystallization from water.

No control experiment was done to show that the tritium content of the acetate did not arise from hydroxide ion catalyzed exchange of tritium into the acetate itself. However, it can be calculated from the reported rate constant for abstraction of an α-hydrogen atom from acetate by hydroxide ion at 25° (10^{-6} M^{-1} min^{-1})[11] that under our conditions this reaction accounts for less than 0.01% of the tritium content of the acetate. Moreover, in all these experiments because of the rapid hydrolysis of ethyl thioacetate, all the acetate existed in the basic tritiated water for at least 8 min out of the total 10-min reaction period, and yet the fraction of tritium incorporated was independent of the concentration of hydroxide ion (Table I).

In the above experiments radioactivity was determined with a Packard Model 577 liquid scintillation counter. Usually 0.2-ml aliquots of the various solution were counted in 15 ml of scintillator solution (4 g of 2,5-diphenyloxazole, 100 mg of 1,4-bis-2(5-phenyloxazolyl)benzene, 125 ml of diethylene glycol dimethyl ether, 750 ml of dioxane, 125 ml of anisole).

Results

Hydrolysis of Ethyl N,N-Dimethylthioacetimidate. At alkaline pH the products of the hydrolysis of ethyl N,N-dimethylthioacetimidate are N,N-dimethylacetamide and ethanethiol (see Experimental Section). This result agrees with the reports[12] that quaternary salts of esters of thioimidic acids form amide and thiol upon basic hydrolysis. The products of the hydrolysis under acid conditions have not been determined, but probably are in part or entirely ethyl thioacetate and dimethylammonium ion, since quaternary salts of esters of thioimidic acids are known to yield thiol ester and amine upon acid hydrolysis.[12b,c,13]

The rates of hydrolysis of ethyl N,N-dimethylthioacetimidate were measured by following the disappearance of the compound spectrophotometrically. The disappearance of the compound was slightly accelerated by the buffers which were used. Plots of the observed first-order rate constants against the concentration of the basic species in the buffers at several buffer ratios were parallel, and thus catalysis is by the basic species. Figure 1 illustrates this catalysis with the data for acetate ion. The following second-order rate constants were obtained at 25° and 0.5 M ionic strength (in units of M^{-1} min^{-1}): acetate ion, 4.0 × 10^{-4}; imidazole, 5.3 × 10^{-3}; phosphate dianion, 11 × 10^{-3}; and triethylenediamine, 0.20. The pH–rate profile for hydrolysis (Figure 2), which was constructed from values of the rate constants obtained upon extrapolation of the values for k_{obsd} to zero buffer concentration, shows that the rate law for hydrolysis has a pH-independent term and a term for catalysis by hydroxide ion. The values of the rate constants for these terms are 8.8 × 10^{-5} min^{-1} and 4.2 × 10^{3} M^{-1} min^{-1} (based upon the activity of hydroxide ion), respectively. These values are very close to those reported for the hydrolysis of 2,3-dimethyl-Δ^2-thiazoline perchlorate at 25° (17 × 10^{-5} min^{-1} and 13 × 10^{3} M^{-1} min^{-1}).[12b]

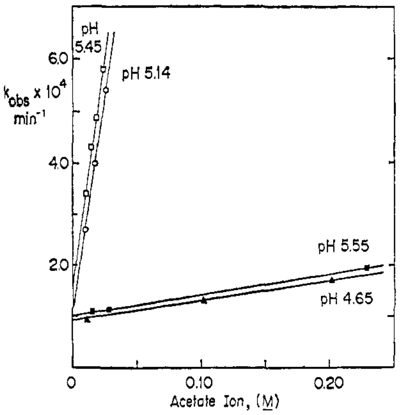

Figure 1. Rates of hydrolysis and iodination of ethyl N,N-dimethylthioacetimidate in potassium acetate buffers, at 25° and 0.5 M ionic strength. The buffer ratios expressed as per cent base were: for hydrolysis, 50% (▲), 90% (■); for iodination, 80% (○), 90% (□).

Kinetics of Enamine Formation from Ethyl N,N-Dimethylthioacetimidate. The rate of reaction of iodine with excess ethyl N,N-dimethylthioacetimidate is independent of the concentration of iodine and directly proportional to the concentration of the iminium thiol ester (see Experimental Section). Moreover, the reaction is markedly catalyzed by carboxylate bases. This catalysis is illustrated with the data for acetate ion in Figure 1 which shows that the plots of k_{obsd} against the concentration of acetate ion at two buffer ratios are parallel. The second-order rate constants obtained for general base catalysis of the reaction with iodine at 25° and 0.5 M ionic strength are: acetate ion, 1.6 × 10^{-2} M^{-1} min^{-1}; succinate dianion, 6.5 × 10^{-2} M^{-1} min^{-1}; and 1,1-cyclobutanedicarboxylate dianion, 10 × 10^{-2} M^{-1} min^{-1}. When the rate constants that are given by extrapolation of the values of k_{obsd} to zero buffer concentration at each buffer ratio are plotted against the activity of hydroxide ion (Figure 3), it is evident that the rate law for the reaction also contains a pH-independent (water) term and a term for hydroxide ion catalysis. The values of the rate constants for these terms are 9 × 10^{-5} min^{-1} and 2.4 × 10^{4} M^{-1} min^{-1}, respectively.

The kinetics of the reaction with iodine resemble those for the iodination of ketones, a reaction which is well known to proceed by general base catalysis of the

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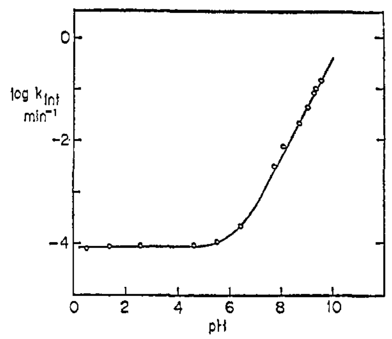
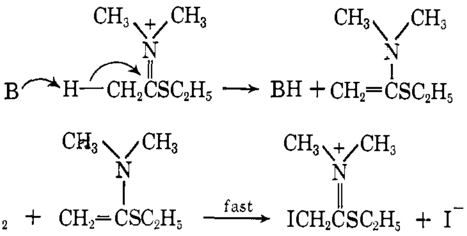


Figure 2. pH-rate profile for the hydrolysis of ethyl N,N-dimethylthioacetimidate at 25° and 0.5 M ionic strength. The buffers used at the various pH values were: hydrochloric acid, 0.54–2.60; potassium acetate, 4.65–5.55; potassium 1,1-cyclobutanedicarboxylate, 6.45; imidazole hydrochloride, 7.78–8.14; triethylenediamine hydrochloride, 8.74–9.33; potassium carbonate, 9.30–9.56. The values of k_{int} are the intercepts which are obtained upon extrapolation of the values for k_{obsd} to zero buffer concentration.

formation of the enolate anion in the rate-determining step followed by rapid reaction of the anion or the enol itself with iodine.[14] By analogy, in the present case there is general base catalysis of enamine formation in the rate-determining step followed by reaction of the enamine with iodine[15] (eq 1, B = H_2O, OH^-, buffer bases).



$$B + H\text{—}CH_2\overset{\overset{CH_3\diagdown\overset{+}{N}\diagup CH_3}{\|}}{C}SC_2H_5 \longrightarrow BH + CH_2{=}\overset{\overset{CH_3\diagdown N\diagup CH_3}{|}}{C}SC_2H_5$$

$$I_2 + CH_2{=}\overset{\overset{CH_3\diagdown N\diagup CH_3}{|}}{C}SC_2H_5 \xrightarrow{\text{fast}} ICH_2\overset{\overset{CH_3\diagdown\overset{+}{N}\diagup CH_3}{\|}}{C}SC_2H_5 + I^- \qquad (1)$$

If the formation of the monoiodinated derivative of ethyl N,N-dimethylthioacetimidate is the only reaction that is consuming iodine, then the rate constants given above, which were measured by following the disappearance of iodine, are equal to the rate constants for enamine formation. However, it is not certain that this is the case. The iminium thiol ester may undergo successive iodinations because of more rapid enamine formation from the mono- and diiodo derivatives. In addition, ethanethiol, which is one of the possible products of the hydrolysis of the iminium thiol ester and of the iodinated derivatives which form from it, reacts rapidly with iodine in the stoichiometry of 2 mol of ethanethiol/mol of iodine (see Experimental Section). In this regard it should be noted that even if the products of hydrolysis of ethyl N,N-dimethylthioacetimidate in the pH range from 3 to 7 were entirely ethanethiol and N,N-dimethylacetamide, the reaction between ethanethiol and iodine can only account for a fraction of the iodine consumption, since the rates of iodine disappearance are always equal to (Figure 3, pH-independent reaction) or greater than (Figures 1 and 3, buffer bases and hydroxide ion) the rates of hydrolysis. As a consequence of these possibilities the rate constants

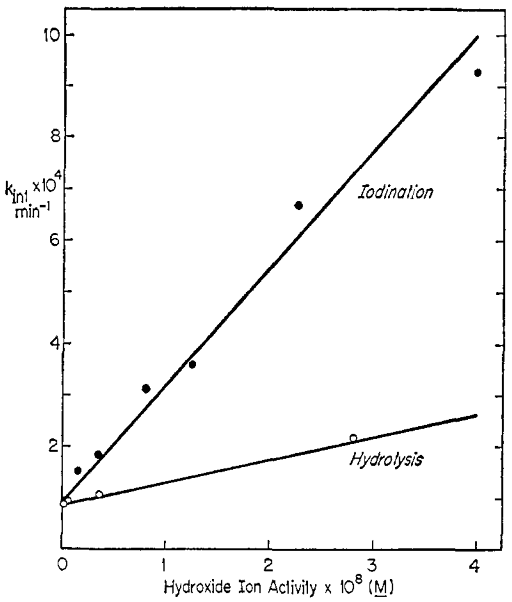


Figure 3. Dependence of the rates of iodination and hydrolysis of ethyl N,N-dimethylthioacetimidate upon the activity of hydroxide ion, at 25° and 0.5 M ionic strength. The buffers used at the various pH's were: for iodination: hydrochloric acid, 2.82; potassium acetate, 5.14–5.45; potassium succinate, 6.10; and potassium 1,1-cyclobutanedicarboxylate, 5.90–6.60; for hydrolysis: hydrochloric acid, 0.5–2.6; potassium acetate, 4.65–5.55; and potassium 1,1-cyclobutanedicarboxylate, 6.45. The values of k_{int} are the intercepts which are obtained upon extrapolation of the values of k_{obsd} to zero buffer concentration. The slope of the plot for hydrolysis is the one calculated from the more extensive data shown in Figure 2.

derived from the disappearance of iodine may be greater than the actual rate constants for enamine formation by as much as a factor of about eight in the case of catalysis by water and about four in the case of catalysis by carboxylate bases and hydroxide ion (but see below the comparison with the rate constant from hydrogen–deuterium exchange).

The rate of enamine formation at alkaline pH values was also determined by carrying out the hydrolysis of ethyl N,N-dimethylthioacetimidate in deuterium oxide and measuring the deuterium content in the α position of the product, N,N-dimethylacetamide. Under these conditions the kinetic scheme for simultaneous hydrogen–deuterium exchange and hydrolysis is approximated by

$$\text{HOD} + \text{C} \underset{k_r^H}{\overset{k_f^H}{\rightleftharpoons}} \overset{+}{\text{C}}\text{-H} + \text{OD}^- \xrightarrow{k_h} \text{P-H}$$

$$\text{DOD} + \text{C} \underset{2k_r^D}{\overset{k_f^D}{\rightleftharpoons}} \overset{+}{\text{C}}\text{-D} + \text{OD}^- \xrightarrow{k_h} \text{P-D} \qquad (2)$$

where C^+H, C, and P are the iminium thiol ester, the enamine, and N,N-dimethylacetamide, respectively, and the rate constants refer to the reactions of each α-hydrogen atom. This scheme neglects secondary deuterium isotope effects upon the rates of hydrolysis and of hydrogen–deuterium exchange of the partially deuterated iminium thiol ester. This neglect should not introduce a large error, since the secondary deuterium isotope effects which have been measured for similar reactions are small.[16] Use of the steady-state

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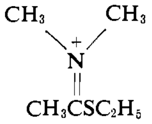
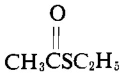
(14) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 140–145.

(15) The mechanism is written with I_2 as the iodinating species. Probably some iodination also occurs by the species I_3^- and I_2Cl^-; see R. P. Bell and D. C. Vogelsong, *J. Chem. Soc.*, 243 (1958).

(16) k_H/k_D for the alkaline hydrolysis of ethyl acetate and ethyl trideuterioacetate at 25° is 0.9 (M. L. Bender and M. S. Feng, *J. Am. Chem.*

Table I. Rates of Exchange of the α Hydrogens of Ethyl N,N-Dimethylthioacetimidate and Ethyl Thioacetate at 25°

Reactant	Initial concn, M	Solvent	k_h', min^{-1}	k_h, M^{-1} min^{-1}	Fraction of exchange	k_f, M^{-1} min^{-1}
 $CH_3C(=N^+(CH_3)_2)SC_2H_5$	0.02	0.002 M NaDCO$_3$ in D$_2$O, pD 9.93^a	0.11^b	$9.4 \times 10^{3\,c}$	0.62^d	$1.52 \times 10^{4\,e}$
	0.01	0.001 M NaDCO$_3$–0.01 M KCl in D$_2$O, pD 10.20^a	0.23^b	$8.4 \times 10^{3\,c}$	0.62^d	$1.36 \times 10^{4\,e}$
 $CH_3C(=O)SC_2H_5$	0.017	0.17 M NaOH–0.17 M NaCl in ^{3}HHO, 205,000 cpm/μatom of H		5.9^f	$4.3 \times 10^{-3\,g}$	$2.5 \times 10^{-2\,h}$
	0.017	0.34 M NaOH in ^{3}HHO, 190,000 cpm/μatom of H			$5.1 \times 10^{-3\,g}$	$3.0 \times 10^{-2\,h}$
	0.033	0.17 M NaOH in ^{3}HHO, 176,000 cpm/μatom of H			$5.0 \times 10^{-3\,g}$	$3.0 \times 10^{-2\,h}$

[a] Maintained by the addition of NaOD with the pH-Stat. [b] Observed first-order rate constant for hydrolysis, determined from the consumption of base. [c] $k_h = k_h'/(OD^-)$, from $(OD^-)(D_3O^+) = 1.54 \times 10^{-15}$. [d] $[P–D]_\infty/[CH]_0$, see text. [e] Second-order rate constant for the abstraction of each α hydrogen of ethyl N,N-dimethylthioacetimidate by deuterioxide ion (k_f^H in eq 2), calculated with eq 3 in the text. [f] For alkaline hydrolysis, see Experimental Section. [g] Specific activity of each α hydrogen of acetate/specific activity of hydrogen in water, both in cpm/μatom. [h] Second-order rate constant for the abstraction of the α-tritium atom of $^3HCH_2C(=O)SC_2H_5$ by hydroxide ion (k_f^T in eq 4), calculated with eq 6 in the text.

approximation for the concentration of the enamine allows the derivation of the relationship (eq 3) between the initial concentration of α-hydrogen atoms ($[C–H]_0 = 3 \times$ the initial concentration of iminium thiol ester), the concentration of α-deuterium atoms after complete hydrolysis ($[P–D]_\infty$), and the rate constants.

$$\frac{[P–D]_\infty}{[C–H]_0} = \frac{k_f^H}{k_f^H + k_h} \tag{3}$$

In the derivation the term $k_r^H[HOD][C]$ was omitted, since in water of 99.7 atom % deuterium its value would only be 0.03 that of the term $k_r^D[DOD][C]$ even if the isotope effect k_r^H/k_r^D were as large as 10. The average value of the rate constants found for the abstraction of each α proton from ethyl N,N-dimethylthioacetimidate in D_2O by deuterioxide ion is 1.42×10^4 M^{-1} min^{-1} (Table I). The value for the corresponding proton transfer to hydroxide ion in H_2O can be estimated as 9.6×10^3 M^{-1} min^{-1} on the basis of the fact that proton abstraction from acetone is 1.5 times faster with deuterioxide ion in D_2O than with hydroxide ion in H_2O.[17] This value is close to that of 8×10^3 M^{-1} min^{-1} for the abstraction of each α-hydrogen atom which is obtained from the rates of iodination under the assumption that iodine is consumed only by reaction with the enamine form of the iminium thiol ester.

Proton Transfer from the α Carbon of Ethyl Thioacetate to Hydroxide Ion. The rate of proton transfer from the α carbon of ethyl thioacetate to hydroxide ion was determined by carrying out the alkaline hydrolysis in water labeled with tritium tracer and measuring the amount of tritium in the product, acetic acid. The kinetic scheme for simultaneous tritium (T) incorporation and hydrolysis is

$$\begin{gathered} HOH + C^- \underset{2k_r^H}{\overset{k_f^H}{\rightleftharpoons}} C–H + OH^- \xrightarrow{k_h} P–H \\ TOH + C^- \underset{k_r^T}{\overset{k_f^T}{\rightleftharpoons}} C–T + OH^- \xrightarrow{k_h} P–T \end{gathered} \tag{4}$$

where C^-, C–H, and P here represent the carbanion of ethyl thioacetate, ethyl thioacetate, and acetate, respectively, and the rate constants are in terms of the reactions of each α-hydrogen atom. This scheme yields the following expression for the concentration of α-tritium atoms after complete hydrolysis ($[P–T]_\infty$).

$$[P–T]_\infty = \frac{k_r^T k_f^H[TOH][CH]_0}{2(k_h + k_f^T)k_r^H[H_2O]} \tag{5}$$

For a similar tritium–hydrogen exchange reaction it has been shown that the equilibrium constant for tritium incorporation ($2[C–T][HOH]/[C–H][TOH] = k_f^H k_r^T/k_f^T k_r^H$) has a value very close to one.[18] Consequently eq 5 reduces to

$$\frac{[P–T]_\infty}{[CH]_0} = \frac{k_f^T[TOH]}{(k_h + k_f^T)2[H_2O]} \tag{6}$$

in which $[P–T]_\infty/[CH]_0$ and $[TOH]/2[H_2O]$ can be taken as the specific activities (cpm/μatom of hydrogen) of each α-hydrogen atom of the acetate and of the medium water, respectively. It was found, in agreement with the kinetic scheme, that extent of tritium incorporation was independent of the concentration of hydroxide ion (Table I). The average value of k_f^T is 2.8×10^{-2} M^{-1} min^{-1}. This value is about the same as those reported for abstraction of an α-tritium atom from substituted acetophenones by hydroxide ion, and for that reaction the value of the isotope effect k_f^H/k_f^T has been determined to be about 14.[19] Consequently, the

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Soc., **82**, 6318 (1960)). The rate of abstraction of deuterium from $C_6H_5CH_2D$ by lithium cyclohexylamide is 1.3 times greater than the rate of abstraction of each deuterium from $C_6H_5CD_3$ (A. Streitwieser, Jr., and D. E. Van Sickle, *J. Am. Chem. Soc.*, **84**, 254 (1962)).

(17) Y. Pocker, *Chem. Ind.* (London), 1383 (1959).

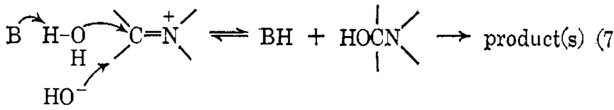
(18) S. V. Rieder and I. A. Rose, *J. Biol. Chem.*, **234**, 1007 (1959).

(19) J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, **63**, 111 (1967).

estimated value of the rate constant at 25° for transfer of each α-hydrogen atom of ethyl thioacetate from carbon to hydroxide ion is 0.4 M^{-1} min^{-1}.

Discussion

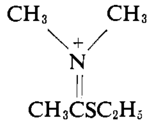
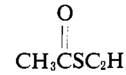
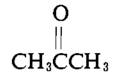
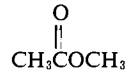
The kinetics of the hydrolysis of a number of other iminium compounds (thioimidates,[12b,c,20,21] 2-methyl-5,6-dihydro-4H-1,3-thiazine,[12b] Schiff bases,[22,23] imidates[24-26]) have been thoroughly investigated. A general mechanism which provides a description of the hydrolysis of all these compounds is hydration of the iminium function by general base catalysis (B = water, buffer bases) and by direct nucleophilic attack by hydroxide ion followed by breakdown of the hydrate to product(s) (eq 7). It should be noted that this mechanism is written here in an incomplete form which does not specify the details of the decomposition of the tetrahedral intermediate to product(s). For many of these iminium compounds it has been found that the formation of the hydrate is the rate-determining step under weakly acidic, neutral, and basic conditions, but that the decomposition of a neutral form of the tetrahedral intermediate is rate limiting under more acidic conditions. This change in rate-determining step has been indicated by a decrease in the rate of hydrolysis in stronger acid. The pH–rate profile for the hydrolysis of ethyl N,N-dimethylthioacetimidate shows no decrease in rate in hydrochloric acid as strong as 0.5 M, and thus there is no evidence for a change in rate-determining step under our conditions. The kinetics of hydrolysis are consistent with rate-limiting hydration according to eq 7 over the entire pH range studied. The conclusion that the buffer bases (acetate, phosphate dianion, imidazole, triethylenediamine) act as general base rather than nucleophilic catalysts is supported by the fact that the Brønsted plot (log k $vs.$ pK_a') of the second-order rate constants for the bases is approximately linear with a slope of about 0.6; for nucleophilic catalysis the rate of imidazole attack on esters is about 10^3 times the rate of phosphate dianion attack, but for general base catalysis the rates are similar.[27] Because our results show that enamine formation occurs more rapidly than the hydrolysis of N,N-dimethylthioacetimidate, other mechanisms for hydrolysis which proceed by an elimination of the ethanethiol from the enamine or the iminium compound itself to yield as an intermediate the dimethyliminium derivative of ketene, $CH_2{=}C{=}N^+(CH_3)_2$, can be envisioned. However, such alternative mechanisms cannot account for the thiol ester as a product of hydrolysis of iminium thiol esters under acidic conditions,[12b,c,13] and, in general, seem unlikely because the kinetics of hydrolysis of 2-aryl-Δ^2-thiazolines and Δ^2-thiazoline itself, which are compounds that cannot form an enamine, are very similar to the kinetics of hydrolysis of 2-methyl-Δ^2-thiazoline.[21]



(7)

The abstraction of each α-hydrogen atom from ethyl thioacetate by hydroxide ion occurs one-fourth as rapidly as the abstraction from acetone and about ten times as fast as the abstraction from methyl acetate (Table II). Since the inductive effects of the $-C({=}O)CH_3$, $-C({=}O)SC_2H_5$, and $-C({=}O)OCH_3$ groups are nearly the same,[28] this order of kinetic acidities reflects the relative contribution of the resonance form $CH_2{=}C({-}O^-)X$ in the incipient carbanions. That this contribution is greatest with acetone and least with methyl acetate is presumably a result of the fact that the extent of stabilization of the reactant by the resonance form $CH_3C({-}O^-){=}X^+$ is greatest with methyl acetate and least with acetone.[28-30] This explanation also accounts for the order for the thermodynamic acidities of the α hydrogens which has been found to be ketone $\geq$ thiol ester > oxygen ester.[3,30]

Table II. Rate Constants for Proton Transfer from α Carbon to Hydroxide Ion, at 25°

Reactant	k,[a] M^{-1} min^{-1}	Ref
 $CH_3\overset{\overset{+}{N}(CH_3)_2}{\overset{\Vert}{C}}SC_2H_5$	9×10^3	b
 $CH_3\overset{O}{\overset{\Vert}{C}}SC_2H_5$	0.4	b
 $CH_3\overset{O}{\overset{\Vert}{C}}CH_3$	1.7	c
 $CH_3\overset{O}{\overset{\Vert}{C}}OCH_3$	≈0.03	d

[a] For the abstraction of each α hydrogen. [b] This work. [c] R. P. Bell and H. C. Longuet-Higgins, *J. Chem. Soc.*, 636 (1946). [d] An estimate based on the following information. The rate constant for proton transfer from methyl acetate to methoxide ion in methanol at 35° is 7.6×10^{-2} M^{-1} min^{-1} per α-hydrogen atom (J. Hine, L. G. Mahone, and C. L. Liotta, *J. Am. Chem. Soc.*, **89**, 5911 (1967)); the rate constant for catalysis of the isomerization between (−)-menthone and (+)-isomenthone by methoxide ion in methanol is nearly the same as that for catalysis by methoxide and hydroxide ions in methanol with 30% water by volume (C. Tubandt, *Ann.*, **354**, 259 (1907)), and the rate constant for catalysis of this isomerization by methoxide ion at 35° is 2.4 times larger than the constant at 25° (J. F. Bunnett and L. A. Retallick, *J. Am. Chem. Soc.*, **89**, 423 (1967)).

Our results show that the $-C({=}N^+)SC_2H_5$ function activates the α-hydrogen atoms for proton transfer to hydroxide ion 2×10^4 times better than the $-C({=}O)SC_2H_5$ function (Table II). The magnitude of this acceleration can be compared with the results of investigations of the relative rates of abstraction of α-hydrogen atoms from aldehydes and ketones and the correspond-

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(20) R. P. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, 29, 3197 (1964).

(21) G. L. Schmir, *J. Am. Chem. Soc.*, 87, 2743 (1965).

(22) E. H. Cordes and W. P. Jencks, *ibid.*, 85, 2843 (1963).

(23) K. Koehler, W. Sandstrom, and E. H. Cordes, *ibid.*, 86, 2413 (1964).

(24) R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, 41, 1662 (1963).

(25) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 3505 (1962).

(26) (a) G. L. Schmir and B. A. Cunningham, *ibid.*, 87, 5692 (1965); (b) B. A. Cunningham and G. L. Schmir, *ibid.*, 88, 551 (1966).

(27) W. P. Jencks and J. Carriuolo, *ibid.*, 83, 1743 (1961).

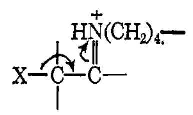
(28) R. N. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, 85, 709 (1963).

(29) M. W. Cronyn, M. P. Chang, and R. A. Wall, *ibid.*, 77, 3031 (1955).

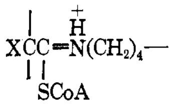
(30) T. C. Bruice in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 423.

ing protonated Schiff bases. Bender and Williams[31] have reported that the reaction $(CH_3)_2C{=}N(H^+)CH_2COO^- + NH_2CH_2COO^- \rightarrow CH_2{=}C(CH_3)N(H)CH_2COO^- + {}^+NH_3CH_2COO^-$ proceeds about 4 × 10^5 times more rapidly than the reaction $(CH_3)_2C{=}O + NH_2CH_2COO^- \rightarrow CH_2{=}C(CH_3)O^- + {}^+NH_3CH_2COO^-$ and from the data of Hine, *et al.*,[32] it can be estimated that the reaction $HO^- + (CH_3)_2CHC(H){=}N(H^+)CH_3 \rightarrow H_2O + (CH_3)_2C{=}CHN(H)CH_3$ occurs 500 times faster than the reaction $HO^- + (CH_3)_2CHCHO \rightarrow H_2O + (CH_3)_2C{=}CHO^-$. These ratios are somewhat uncertain because their calculations are based on estimated values for the acid dissociation constants of the protonated Schiff bases. Moreover, even if account is made for the imprecision in these dissociation constants, there appear to be some considerable unexplained discrepancies between the results of Bender and Williams and those of Hine, *et al.* For example, Bender and Williams estimate that the base H_2O abstracts a proton from the α position of $(CH_3)_2C{=}N(H^+)CH_3$ about 10^9 times faster than from the α position of acetone itself, whereas the data of Hine, *et al.*, indicate a rate acceleration of only about 10^3 in the analogous comparison between $(CH_3)_2CHC(H){=}N(H^+)CH_3$ and isobutyraldehyde.

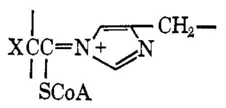
The enzymatic decarboxylation of acetoacetate[33] and the enzymatic dealdolization of several β-hydroxy ketones[34] have been shown to be catalyzed by Schiff base intermediates formed between the keto group of the substrates and the ϵ-amino group of a lysine residue of the enzymes, as follows



where for decarboxylation X = ^-O_2C in the forward reaction and H in the reverse and for dealdolization X = R_2COH in the forward direction and H in the reverse. Also the enzymatic dehydration of 2-keto-3-deoxy-L-arabonate to α-ketoglutarate semialdehyde proceeds by way of a Schiff base intermediate.[35] Other enzymes catalyze reactions similar to these with thiol esters, usually of coenzyme A (HSCoA), as substrates ($>CXC({=}O)SCoA$).[36] Our results suggest that some of these enzymatic reactions may be catalyzed by the formation of an iminium thiol ester intermediate from the substrate thiol ester and the ϵ-amino group of a lysine residue, I, or possibly the imidazole group of a histidine residue, II.

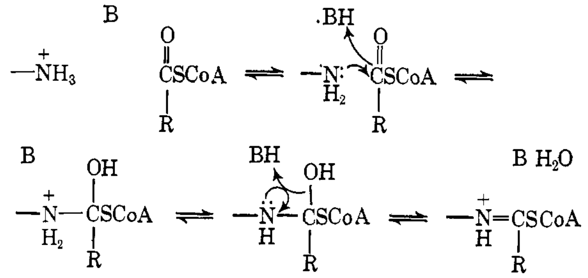


I



II

The formation of the lysine iminium thiol ester is feasible on thermodynamic grounds, since the equilibrium constant for the formation of 2-methyl-Δ^2-thiazolinium ion from S-acetylmercaptoethylammonium ion is about 0.1.[12b] Moreover, the extensive kinetic studies of Martin, *et al.*,[12b,20,37] on the interconversions of 2-methyl-Δ^2-thiazoline, S-acetylmercaptoethylamine, and N-acetylmercaptoethylamine have shown that with sufficiently strong acid catalysis S-acetylmercaptoethylammonium ion forms 2-methyl-Δ^2-thiazolinium ion more rapidly than it rearranges to N-acetylmercaptoethylamine. Thus, although the product of the reaction of an amine with a thiol ester under weakly acidic, neutral, and basic conditions is the amide,[8,37] it seems possible that selective general acid catalysis by an enzyme could alter this pathway and allow facile formation of the iminium thiol ester instead of the amide. An example of such a mechanism is given in eq 8, where BH is a general acid of the enzyme. This type



(8)

of mechanism avoids tetrahedral intermediates of the form B···HOCR(NH–)SCoA and $^-$OCR(NH–)SCoA which would decompose to yield the amide rather than the thiol ester.[12c] The suggestion that an iminium thiol ester intermediate from imidazole (II) might function in enzymatic catalysis has some chemical precedent: Bender and Williams found that imidazolium ion is about $10^{3.5}$ times better a catalyst for the iodination of acetone than is predicted from its acidity and the Brønsted plot for carboxylic acid catalysts, and they have reasonably interpreted this extraordinary catalytic effectiveness as the result of the formation of the cationic Schiff base of acetone and imidazole followed by enaminization.[31]

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(31) M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966).

(32) (a) J. Hine, B. C. Menon, J. H. Jenson, and J. Mulders, *ibid.*, **88**, 3367 (1966); (b) J. Hine, F. C. Kokesh, K. E. Hampton, and J. Mulders, *ibid.*, **89**, 1205 (1967); (c) J. Hine, J. Mulders, J. G. Houston, and J. P. Idoux, *J. Org. Chem.*, **32**, 2205 (1967).

(33) R. A. Laursen and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3426 (1966), and references therein.

(34) (a) O. M. Rosen, P. Hoffee, and B. L. Horecker, *J. Biol. Chem.*, **240**, 1517 (1965), and references therein; (b) I. A. Rose and E. L. O'Connell, *Arch. Biochem. Biophys.*, **118**, 758 (1967); (c) R. D. Kobes and E. E. Dekker, *Biochem. Biophys. Res. Commun.*, 27, 607 (1967).

(35) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, 242, 2751 (1967).

(36) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 259–263, for a compilation.

(37) (a) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959); (b) R. B. Martin and R. I. Hedrick, *ibid.*, **84**, 106 (1962)