aromatic H), 3.86 and 3.77 (s, s, 3, OCH_3), 3.50–4.00 (m, 4, $CH_2 \times 2$), 1.80–2.20 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{15}H_{18}Cl_2N_2O_2$: C, 54.72; H, 5.51: N, 8.51; Cl, 21.54. Found: C, 54.49; H, 5.77; N, 8.22; Cl, 21.78.

In the same manner, other amidine (**3b–e**) hydrochlorides were obtained as a mixture of *Z* and *E* having the ratio shown in Table I. IR and NMR spectra and elemental analyses are shown as follows:

Methyl α-[(Pyrrolidinylmethylene)amino]-p-methylcinnamate (3b) Hydrochloride: IR (Nujol) 1738 (COOMe), 1695 (N=C), 1640 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.70 (br, 1, HCl), 8.70 and 8.47 (broad s, 1, N=CH), 7.26 (s, 1, CH=C), 7.40–8.10 and 7.21 (m, s, 4, aromatic H), 3.40–4.00 (m, 4, $CH_2 \times 2$), 3.80 and 3.70 (s, s, 3, OCH_3), 2.40 and 2.30 (s, s, 3, CH_3), 1.70–2.20 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{16}H_{21}ClN_2O_2$: C, 62.23; H, 6.85; N, 9.07; Cl, 11.48. Found: C, 62.25; H, 6.74; N, 9.15; Cl, 11.71.

Methyl α-[(Pyrrolidinylmethylene)amino]-3,4-methylenedioxycinnamate (3c) Hydrochloride: IR (Nujol) 1737 (COOMe), 1700 (N=C), 1640 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.50 (br, 1, HCl), 8.68 and 8.51 (broad s, 1, N=CH), 7.20 (s, 1, CH=C), 6.90 (s, 3, aromatic H), 6.08 (s, 2, OCH_2-O), 3.71 and 3.80 (s, s, 3, OCH_3), 3.10–4.10 (m, 4, $CH_2 \times 2$), 1.60–2.30 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{16}H_{19}ClN_2O_4$: C, 56.72; H, 5.65; N, 8.27; Cl, 10.47. Found: C, 56.48; H, 5.78; N, 8.28; Cl, 10.50.

Methyl α-[(Piperidinomethylene)amino]-p-dimethylaminocinnamate (3d) Dihydrochloride: IR (Nujol) 1730 (COOMe), 1690 (N=C), 1638 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.80 and 9.00 (broad s, 2, HCl × 2), 8.0–8.70 (m, 1, N=CH), 6.80–7.80 (m, 5, CH=C and aromatic H), 3.70 and 3.78 (s, s, 3, OCH_3), 3.50–4.10 (m, 4, $CH_2 \times 2$), 3.02 and 3.08 (s, s, 6, $NCH_3 \times 2$), 1.60–1.90 (m, 6, $CH_2 \times 3$).

Anal. Calcd for $C_{18}H_{27}Cl_2N_3O_2$: C, 55.67; H, 7.01; N, 10.82; Cl, 18.26. Found: C, 55.52; H, 6.96; N, 10.81; Cl, 18.13.

Methyl α-[(Pyrrolidinylmethylene)amino]-β-2-thienylacrylate (3e) Hydrochloride: IR (Nujol) 1710 (COOMe), 1680 (N=C), 1617 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.50 (broad s, 1, HCl), 8.69 (broad s, 1, N=CH), 7.40–7.90 (m, 2, CH=C and thiophene 5-H), 7.40–7.60 (m, 1, thiophene 3 H), 7.00–7.20 (m, 1, thiophene 4 H), 3.82 (s, 3, OCH_3), 3.20–4.00 (m, 4, $CH_2 \times 2$), 1.70–2.20 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{13}H_{17}ClN_2O_2S$: C, 51.91; H, 5.70; N, 9.31; Cl, 11.79; S, 10.66. Found: C, 51.88; H, 5.79; N, 9.18; Cl, 11.91; S, 10.57.

Typical Procedure for Preparation of the Amidine Compound (3a) from Isocyanides (5a). After a mixture of (*Z*)-methyl α-isocyano-*p*-chlorocinnamate ((*Z*)-**5a,** 662 mg, 3 mmol) and pyrrolidine (497 mg, 7 mmol) in methanol (15 mL) was stirred for 5 h at room temperature, the same treatment as described in the one-step reaction was carried out to afford **3a.**

In a similar way, other amidine (**3b–e**) hydrochlorides were prepared in good yields as shown in Table I. The IR and ^1H NMR spectra were in accord with those of **3** hydrochlorides obtained by the one-step reaction.

Acknowledgment. We wish to express our thanks to Dr. Ichiro Chibata, Director and Dr. Muneji Miyoshi, Vice Director of this Research Laboratory for their encouragement in this study.

Registry No.—**2,** 39687-95-1; (*Z*)-**3a,** 68001-91-2; (*E*)-**3a,** 68001-92-3; (*Z*)-**3b,** 68001-93-4; (*E*)-**3b,** 68001-94-5; (*Z*)-**3c,** 68024-33-9; (*E*)-**3c,** 68024-32-8; (*E*)-**3d,** 68001-95-6; **3e,** 68001-96-7; pyrrolidine, 123-75-1; p-chlorobenzaldehyde, 104-88-1; 3,4-methylenedioxybenzaldehyde, 120-57-0; *p*-methylbenzaldehyde, 104-87-0; 4-dimethylaminobenzaldehyde, 100-10-7; 2-thiophenecarboxaldehyde, 98-03-3; piperidine, 110-89-4.

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(12) All the melting points were uncorrected and measured by the use of a Yamato melting point apparatus. Column chromatography was carried out on silica gel (Kieselgel, 0.063–0.200 mm, E. Merck). The IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. The ^1H NMR spectra were obtained using a Hitachi Perkin-Elmer R-20A high-resolution NMR spectrometer with tetramethylsilane as internal standard.

One-Proton Catalysis in the Intermolecular Imidazole-Catalyzed Hydrolysis of Esters and Amides[1]

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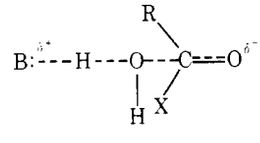
The linear proton inventories observed for the imidazole-catalyzed hydrolysis of both 1-acetylimidazole and ethyl trifluorothiolacetate are interpreted in terms of transition-state structures. The observed solvent isotope effects arise from a single transition-state proton (i.e., one-proton catalysis).

Intermolecular general base catalysis is known to occur in a variety of hydrolytic reactions.[3] A number of bases such as imidazole, acetate, or even water can function as general base catalysts in such reactions. It has been presumed that a typical transition state for such a reaction could be represented as in eq 1.



(1)

Evidence for such transition states comes mainly from Brønsted plots. For example, the logarithms of the second-order rate constants for the hydrolysis of ethyl dichloroacetate catalyzed by oxygen bases bear a linear relationship to the pK_a of the bases. The Brønsted β value is 0.47.[4] Interestingly, the rate constant for the "water" reaction also falls on the Brønsted line suggesting that water also functions as a general base in this reaction. In fact, considerable evidence has accumulated which indicates that the neutral,water-catalyzed hydrolysis of esters, amides, and carbonates involves transition states such as those shown in eq 2. Most of the support

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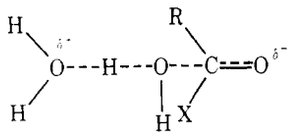
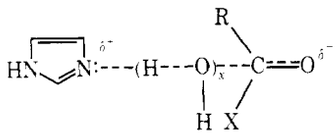
for such transition state structures comes from Brønsted plots and proton inventories.[5]



(2)

Although the one-proton transition state of eq 1 (so-called because one proton is in flight in the transition state) is well accepted there is little supportive evidence for it other than Brønsted plots. Multiple proton catalysis involving a general base (e.g., imidazole) and several water molecules such as that shown in eq 3 could also explain much of the collected data. One can differentiate these transition state structures using the proton inventory technique. Proton inventories have been used to confirm one-proton mechanisms for the hydrolysis of *o*-dichloracetylsalicyclic acid[6] and for the deacetylation of acetyl-α-chymotrypsin.[7] It is important to be able to distinguish between the one-proton mechanism of eq 1 and the multiproton mechanism of eq 3 because of the important role



(3)

as a general base catalyst thought to be played by histidine imidazole in several hydrolytic enzymes.[7] Toward this end we have used the proton inventory to investigate the imidazole-catalyzed hydrolysis of 1-acetylimidazole and ethyl trifluorothiolacetate as models for these processes.

Experimental Section

Materials. 1-Acetylimidazole and ethyl trifluorothiolacetate were commercial products which were purified as previously reported.[5b,d] Imidazole was purified by repeated recrystallization from benzene. N^1-Imidazole-*d* was prepared as previously reported.[8] Deuterium oxide (99.8 atom % deuterium, Aldrich) was purified by distillation in an all-glass apparatus before use. Water was glass distilled before use. Deuterium chloride (20% solution in D_2O, Aldrich) was used as obtained.

The stock 1:1 imidazole–imidazolium ion buffer solution was prepared by half neutralization of the necessary amount of imidazole with 0.10 M HCl solution and dilution to 0.20 M. The ionic strength was maintained at 1.0 M with added potassium chloride. Solutions of lower buffer concentration were prepared from the stock buffer solution by dilution with 1.0 M potassium chloride solution. The stock buffer solution in deuterium oxide was prepared in the same manner using N^1-imidazole-*d*, 0.10 M DCl solution, and a 1.0 M potassium chloride solution in deuterium oxide. Reactions in H_2O–D_2O mixtures were run using appropriate volumes of the stock buffer solutions. The pH of the solutions was measured before and after each run using a Corning pH meter 130 equipped with a combination electrode.

Kinetics. The hydrolysis of 1-acetylimidazole and that of ethyl trifluorothiolacetate were followed at 245 nm as reported earlier.[5b,d] Pseudo-first-order rate constants were determined from plots of log $(A_t - A_\infty)$ vs. time and were confirmed in some cases using a nonlinear least-squares computer program which calculates first-order rate constants from given time and absorbance values. The second-order rate constants for the imidazole-catalyzed hydrolysis were obtained as the slopes of plots of the pseudo-first-order rate constants vs. the free imidazole concentration.

Results

1-Acetylimidazole. Figure 1 shows the plots of observed pseudo-first-order rate constants for the imidazole-catalyzed hydrolysis of 1-acetylimidazole vs. free imidazole concentration in H_2O–D_2O mixtures of atom fraction deuterium, *n*, at 25 °C. The second-order rate constants k_2 were obtained as the slopes of these linear plots and are collected in Table I. The value of k_2 in H_2O obtained in the present study was 0.12 M^{-1} m^{-1}. This value is in good agreement with the literature value of 0.14 M^{-1} m^{-1}.[9] The measured solvent isotope effect,

Table I. Values of k_2 for the Imidazole-Catalyzed Hydrolysis of 1-Acetylimidazole in H_2O–D_2O Mixtures of Atom Fraction Deuterium *n* at 25.00 ± 0.05 °C[a]

atom fraction of deuterium (*n*)	10^4k_2, M^{-1} m^{-1}	10^4k_2 (calcd),[b] M^{-1} m^{-1}
0.000	1176 ± 48[c]	1185
0.249	980 ± 30	976
0.330	920 ± 18	905
0.495	776 ± 24	766
0.659	602 ± 14	627
0.742	556 ± 12	556
0.989[d]	354 ± 4	347

[a] Ionic strength maintained at 1.0 M with KCl. [b] Calculated based on the model of eq 6. [c] Error limits are standard deviations. [d] Atom fraction of deuterium in "100%" deuterated buffer solution as determined by Mr. Josef Nemeth.[15]

Table II. Values of k_2 for the Imidazole-Catalyzed Hydrolysis of Ethyl Trifluorothiolacetate in H_2O–D_2O Mixtures of Atom Fraction Deuterium *n* at 25.00 ± 0.05 °C[a]

atom fraction of deuterium (*n*)	k_2, M^{-1} m^{-1}	k_2(calcd),[b] M^{-1} m^{-1}
0.000	4.29 ± 0.12[c]	4.34
0.245	3.65 ± 0.10	3.64
0.489	2.96 ± 0.08	2.94
0.734	2.17 ± 0.06	2.23
0.978[d]	1.51 ± 0.04	1.53

[a] Ionic strength maintained at 1.0 M with KCl. [b] Calculated based on the model of eq 8. [c] Error limits are standard deviations. [d] Atom fraction of deuterium in "100%" deuterated buffer solution as determined by Mr. Josef Nemeth.[15]

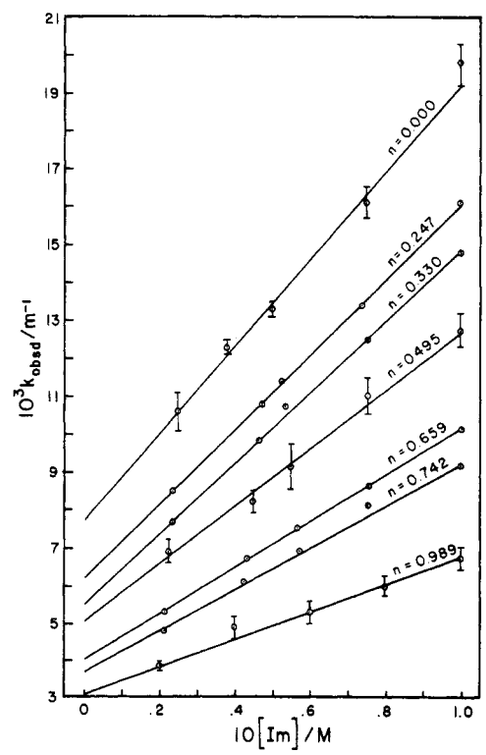


Figure 1. Plots of k_{obsd} vs. free imidazole concentration for the hydrolysis of 1-acetylimidazole in H_2O–D_2O mixtures of atom fraction deuterium, *n*, at 25.00 ± 0.05 °C. Points with error bars represent the average of from three to five runs while those without represent single determinations.

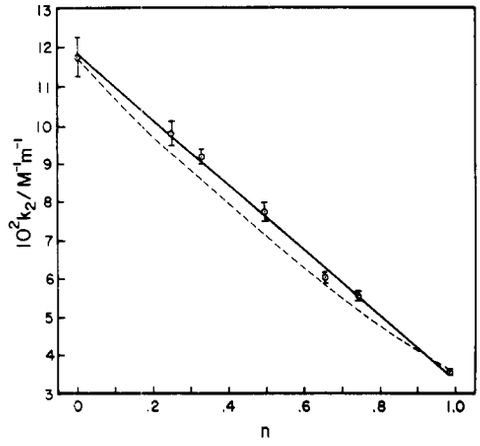


Figure 2. Dependence of the second-order rate constants, k_2, for the imidazole-catalyzed hydrolysis of 1-acetylimidazole on the atom fraction of deuterium, n, in the solvent. The data are taken from Table I. The solid line is calculated based upon the one-proton model represented by eq 6 and represents a linear least-squares fit of the experimental data. The dashed line is based upon the two-proton model represented by eq 9.

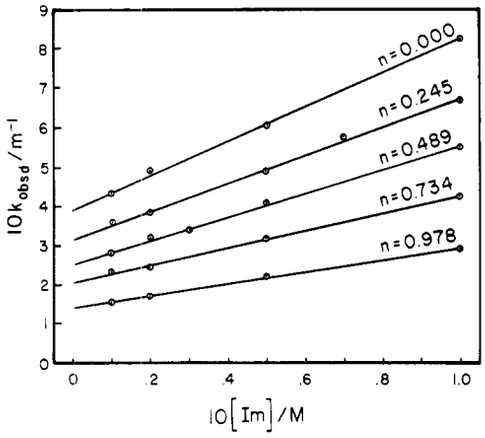


Figure 3. Plots of k_{obsd} vs. free imidazole concentration for the hydrolysis of ethyl trifluorothiolacetate in H_2O–D_2O mixtures of atom fraction deuterium, n, at 25.00 ± 0.05 °C. Each point is the average of three determinations. Where error bars are omitted the circles themselves encompass the error bars.

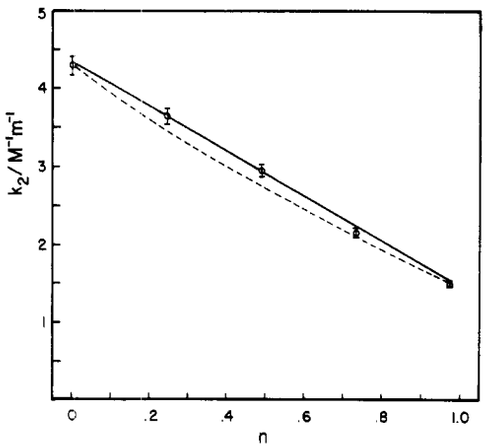


Figure 4. Dependence of the second-order rate constants, k_2, for the imidazole-catalyzed hydrolysis of ethyl trifluorothiolacetate on the atom fraction of deuterium, n, in the solvent. The data are taken from Table II. The solid line is calculated based upon the one-proton model represented by eq 8 and represents a linear least-squares fit of the experimental data. The dashed line is based upon the two-proton model represented by eq 10.

$k_2^{H_2O}/k_2^{D_2O}$, was 3.32. Figure 2 shows the plot of k_2 vs. the atom fraction of deuterium, n, in the solvent for the imidazole-catalyzed hydrolysis.

Ethyl Trifluorothiolacetate. Figure 3 shows the plots of observed pseudo-first-order rate constants for the imidazole-catalyzed hydrolysis of ethyl trifluorothiolacetate vs. free imidazole concentration in H_2O–D_2O mixtures of atom fraction deuterium, n, at 25 °C. Values of k_2 are collected in Table II. The literature value for k_2 at 30 °C is 6.23 M^{-1} m^{-1} which is in good agreement with our value of 4.29 M^{-1} m^{-1} obtained at 25 °C.[10] The measured solvent isotope effect, $k_2^{H_2O}/k_2^{D_2O}$, at 25 °C was 2.84. Figure 4 shows the plot of k_2 vs. the atom fraction of deuterium, n, in the solvent for the imidazole-catalyzed hydrolysis.

Discussion

The proton inventory technique has been successfully used recently to arrive at transition state structures for both model[5,6] and enzymatic reactions.[7,11] The theory of the proton inventory technique has been discussed in detail in these recent publications so the treatment given below is brief.

The technique involves the measurement of reaction rate constants in protium oxide, deuterium oxide, and mixtures of the two. The observed rate constant, k_n, in an H_2O–D_2O mixture of atom fraction deuterium, n, is related to the rate constant, k_0, in pure water by eq 4.

$$k_n = k_0 \prod_i^{TS} (1 - n + n\phi_i^*) \Big/ \prod_j^{RS} (1 - n + n\phi_j) \qquad (4)$$

All exchangeable transition state protons, i, that contribute to the observed solvent isotope effect contribute a term of the form shown in parentheses in the numerator of eq 4. Exchangeable reactant state protons, j, contribute terms of the form shown in parentheses in the denominator of eq 4. Each exchangeable proton is associated with an isotopic fractionation factor defined as in eq 5. These factors express the equilibrium deuterium preference of the exchangeable site, k, in question relative to the deuterium preference of an average solvent site. Fractionation factors less than unity indicate a greater preference for protium than deuterium at the exchangeable site relative to the solvent.

$$\phi_k = ([D]/[H])_k/([D]/[H])_{solvent} \qquad (5)$$

If all the isotopic reactants are solvent molecules then, by definition, $\phi_j = 1$ and the denominator of eq 4 becomes unity. Any isotopic reactants other than solvent molecules having fractionation factors of unity would give the same result. Such is the case here. Thus, we need only be concerned with the numerator of eq 4. Furthermore, if only one proton in the transition state contributes to the overall solvent isotope effect a plot of k_n vs. n will be linear (i.e., one-proton catalysis) except under unlikely conditions.[12] A nonlinear plot of k_n vs. n indicates two or more protons are contributing to the solvent isotope effect (i.e., multiproton catalysis).

The linear dependence of k_2 on n for the imidazole-catalyzed hydrolysis of both 1-acetylimidazole and ethyl trifluorothiolacetate is apparent in Figures 2 and 4. Since there are no reactant state contributions to the isotope effect it is only necessary to formulate a reasonable chemical model consistent with the observed proton inventories for the transition states of the two reactions.

The linear plots of Figures 2 and 4 indicate that the imidazole-catalyzed hydrolysis of both 1-acetylimidazole and ethyl trifluorothiolacetate involves one-proton catalysis. This single proton is responsible for the observed solvent isotope effects of 3.32 and 2.84 respectively for 1-acetylimidazole and ethyl trifluoroacetate hydrolysis.

The solid line of Figure 2 has been drawn based upon eq 6

and is seen to accurately describe the linear proton inventory for the imidazole-catalyzed hydrolysis of 1-acetylimidazole.

$$k_n = 0.1185(1 - n + 0.285n) \quad (6)$$

Equation 6 was obtained by a linear lest-squares fit of the experimental data to the linear form of eq 4 applicable to this study. This form of the equation is seen in eq 7.

$$k_n = k_0 - n(k_0 - k_0\phi^*) \quad (7)$$

A linear least-squares fit of the data to eq 7 using the experimental values of k_n and n allows one to determine the required ϕ^* value. The ϕ^* value determined in this manner was 0.285. Calculated values of k_n based on eq 6 at various n values are included in Table I.

A similar treatment of the data for the imidazole-catalyzed hydrolysis of ethyl trifluorothiolacetate results in eq 8.

$$k_n = 4.34(1 - n + 0.339n) \quad (8)$$

The solid line of Figure 4 is based on this equation and describes the experimental inventory very well. Calculated values of k_n based on eq 8 are included in Table II.

It can easily be shown that multiproton mechanisms are inconsistent with the proton inventories of Figures 2 and 4. For instance, any two-proton model in which both protons contribute equally to the observed solvent isotope effects would generate eq 9 and 10 for the 1-acetylimidazole system and the ethyl trifluorothiolacetate system, respectively.

$$k_n = k_0(1 - n + 0.55n)^2 \quad (9)$$

$$k_n = k_0(1 - n + 0.59n)^2 \quad (10)$$

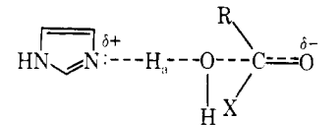
The dashed lines of Figures 2 and 4 are based on these equations. Clearly such multiproton transition states are inconsistent with the observed inventories. It can also be shown that for a transition state in which a very large number of protons each contribute a very small normal isotope effect eq 11 predicts the shape of the proton inventory.

$$k_n = k_0(k_{1.0}/k_0)^n \quad (11)$$

Such "medium effects" represent a net loosening of the binding for a very large number of bulk solvent protons. Substitution of k_0 values and values of n into eq 11 allow one to easily see that such a "medium effect" is also inconsistent with the observed solvent isotope effects.

Conclusion

Clearly then only the one-proton transition state models are consistent with the observed proton inventories for the imidazole-catalyzed hydrolysis of both 1-acetylimidazole and ethyl trifluorothiolacetate. Thus, one can postulate a transition state structure such as that shown in eq 12 for these reactions in which the "in-flight" proton H_a is solely responsible for the observed solvent isotope effect.



(12)

a, R = CH_3; X = 

b, R = CF_3; X = $-SCH_2CH_3$

Huang, Robinson, and Long have studied the intermolecular acetate ion catalyzed mutarotation of tetramethylglucose in H_2O–D_2O mixtures.[13] Their data also fit a linear relationship quite closely suggesting a one-proton mechanism for this reaction. Interestingly, the acetate ion catalyzed hydrolysis of 3,5 dinitroaspirin studied by Gandour and Schowen gave a complex relationship between k_n and n.[14] Nucleophilic catalysis is probably responsible for this complex result. We would like to postulate the generality of transition state structures such as those shown in eq 12 for intermolecular general base catalyzed hydrolysis reactions.

Acknowledgment. Grateful acknowledgment is made to the Robert A. Welch Foundation for support of this work.

Registry No.—1-Acetylimidazole, 2466-76-4; ethyl trifluorothiolacetate, 383-64-2; imidazole, 288-32-4.

References and Notes

(1) Taken in part from the M.S. Thesis of Jacob F. Patterson, Texas A&M University, 1978.
(2) (a) Recipient of a Robert A. Welch Foundation Predoctoral Fellowship; (b) Recipient of a Robert A. Welch Foundation Undergraduate Scholarship.
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