(5.77 g, 48 mmol) in 25 ml of ether. The reaction mixture was stirred for 15 min, and **2** (2.62 g, 16 mmol) in 75 ml of ether was added. The reaction was stirred for 1 hr in the "dark," quenched with excess ammonium chloride, and then processed in the normal manner. Unreacted acetophenone was removed by vacuum distillation. The residue from the distillation was chromatographed on silica gel to give 2.05 g (78.2% recovery) of **2** and 0.71 g (18%) of 2-phenacylquinoline (**5b**), mp 110–113° (lit.[10] mp 114–116°). Spectral characteristics of this material were identical with those of an authentic sample of **5b**.

Reaction of 4b with 2 in the Presence of DNB. To **4b** (48 mmol), prepared as in the preceding experiment from lithium amide (64 mmol) and acetophenone (48 mmol), 0.27 g (1.6 mmol) of DNB was added followed by 2.62 g (16 mmol) of **2** in 75 ml of ether. The reaction mixture was stirred for 1 hr, quenched with excess solid ammonium chloride, and then processed in the usual manner. Glpc analysis of the residual oil indicated that ketone **5b** was produced in less than 1% yield.

Photostimulation of the Reaction of 4b with 2. Just prior to the addition of **2** (2.62 g, 16 mmol) in 75 ml of ether to 48 mmol of **4b** in 500 ml of liquid ammonia under a nitrogen atmosphere, irradiation from a 250-W tungsten lamp was begun. After being stirred for 1 hr, the reaction mixture was quenched with excess solid ammonium chloride and then processed in the usual manner. Chromatography of the residue on silica gel afforded 3.25 g (82.8%) of **5b**.

Acknowledgment. This work was generously supported by the National Institute of Neurological Diseases and Stroke under Grant No. NS 10197. We are indebted to Dr. J. G. Mason for helpful discussions.

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Imidazole-Catalyzed Hydrolysis of Anilides. Nucleophilic Catalysis or Proton-Transfer Catalysis?

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Abstract: Imidazole is found to act as a catalyst for proton transfer and not as a nucleophile in the hydrolysis of trifluoroacetanilides.

The imidazole-catalyzed hydrolysis of esters and amides is of great current interest because of the catalytic role of the imidazole group of histidine-57 in the mechanism of action of chymotrypsin and other proteolytic enzymes.[1] Although both nucleophilic and general base pathways have been observed for ester hydrolysis,[2] buffer catalysis of amide hydrolysis has generally been interpreted as specific base-general acid catalysis.[3] Recently, however, it has been suggested that in the hydrolysis of 2,2,2-trifluoroacetanilides imidazole acts solely as a nucleophile.[4] Furthermore, it was proposed that substantial quantities of the tetrahedral intermediate formed from addition of imidazole accumulate during the reaction.

We now wish to report that the imidazole-catalyzed hydrolysis of *p*-nitro-2,2,2-trifluoroacetanilide (I) shows kinetic behavior which is inconsistent with the proposed nucleophilic mechanism. On the contrary, our results point to general base-catalyzed formation of a tetrahedral intermediate (T^-), coupled with general acid-catalyzed breakdown of this intermediate as being the *only* mechanism for this reaction. We have also reinvestigated the hydrolysis of two of the anilides originally used as a basis for the nucleophilic mechanism and find no evidence for either nucleophilic attack by imidazole or buildup of an intermediate.

Results and Discussion

The hydrolysis of I was followed spectrally at pH 6.55, 7.06, and 7.62 in imidazole buffers at 25.0° and ionic strength of 0.2 (NaCl). Excellent pseudo-first-order kinetics were observed in all cases where the reaction was fol-

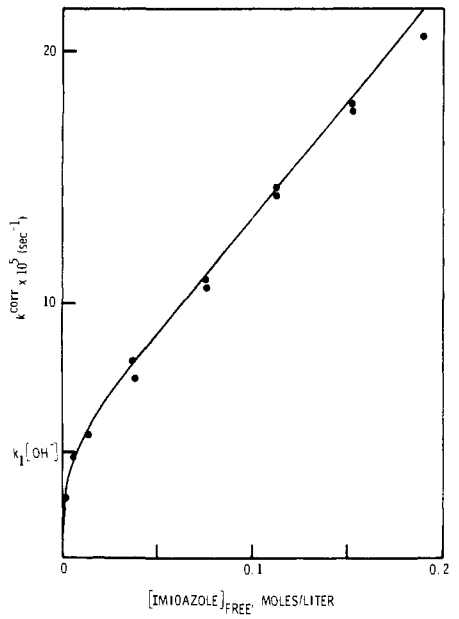


Figure 1. Plot of log k^{corr} for the hydrolysis of *p*-nitrotrifluoroacetanilide *vs.* concentration of free imidazole at pH 7.06 and 25.0°. The line is calculated from eq 2 using the parameters given in the text.

lowed to completion. Some rate constants at low [Im] were obtained by measuring initial rates. The observed rate constants were corrected for ionization of I to its unreactive anion by eq 1 using $pK_a = 8.2$.[3a] A plot of k^{corr} *vs.* the con-

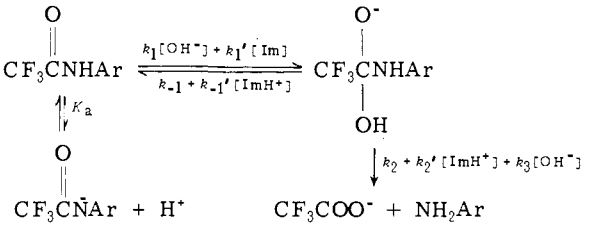
$$k^{corr} = k^{obsd}(1 + (K_a/[H^+])) \quad (1)$$

centration of unprotonated imidazole (Figure 1) may be analyzed in terms of general base-catalyzed formation and general acid-catalyzed breakdown of a tetrahedral intermediate (Scheme I). Application of the steady-state assumption gives eq 2. At low concentrations of imidazole, break-

$$k^{corr} = \frac{(k_1[OH^-] + k_1'[Im])(k_2 + k_2'[ImH^+] + k_3[OH^-])}{k_{-1} + k_{-1}'[ImH^+] + k_2 + k_2'[ImH^+] + k_3[OH^-]} \quad (2)$$

down of T^- is rate determining and catalysis is due to imidazolium ion ($k_2'[ImH^+]$ term). At higher imidazole concentrations, breakdown of T^- becomes faster than its reversion to reactants (*i.e.*, $k_2'[ImH^+] + k_2 + k_3[OH^-] > k_{-1} + k_{-1}'[ImH^+]$), and addition of hydroxide ion becomes the slow step.

Scheme I



The kinetic parameters were evaluated by the following method. At high concentrations of imidazole, eq 2 simplifies to eq 3. Weighted least-squares analysis of plots of k^{corr} *vs.*

$$k^{corr} = k_1[OH^-] + k_1'[Im] \quad (3)$$

[Im] at constant pH and high concentrations of imidazole gives k_1' (slope) and $k_1[OH^-]$ (intercept). The calculated values of k_1 determined in this way are in reasonable agreement (≤30%) with that previously determined[3a] by analysis of the hydroxide ion data alone.

Values for k_2'/k_{-1} were calculated from the rate constants at low imidazole concentrations using eq 4. Equation 4 is obtained by rearranging eq 2, making use of the fact

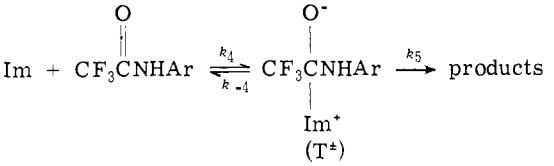
$$\frac{k_2'}{k_{-1}} = \left\{k^{corr}\left(1 + \frac{k_1'[Im]}{k_1[OH^-]} + \frac{k_2 + k_3[OH^-]}{k_{-1}}\right) - (k_1[OH^-] + k_1'[Im])\frac{k_2 + k_3[OH^-]}{k_{-1}}\right\} \times \{(k_1[OH^-] + k_1'[Im] - k^{corr})[ImH^+]\}^{-1} \quad (4)$$

that $k_1[OH^-]/k_{-1} = k_1'[Im]/k_{-1}'[ImH^+]$. The parameters k_2/k_{-1}, k_3/k_{-1}, and k_1 are known from previous work[3a] and an estimate of k_1' is available from eq 3. The ratio k_2'/k_{-1} was then calculated for each point at low imidazole concentrations and averaged. The parameters were then varied slightly (≤20%) to give the best fit to the data.

The above method gave $k_1' = 8.9 \times 10^{-4}\ M^{-1}$ sec^{-1} and $k_2'/k_{-1} = 255$ at pH 7.06 and 160 at pH 7.62. We consider the ratios of k_2'/k_{-1} at pH 7.06 and 7.62 to be indistinguishable due to the difficulty in obtaining precise values for this ratio. k_2'/k_{-1} could not be determined at pH 6.55 from our data.

Our analysis of the kinetic results in terms of Scheme I does not, of course, prove that this mechanism is the correct one. However, the parameters calculated on this basis adequately account for the observed rate constants (Figure 1), showing that Scheme I is consistent with these results. The alternative mechanism, nucleophilic attack with buildup of an intermediate (Scheme II),[4] may be rejected for the fol-

Scheme II



lowing reasons. (1) This mechanism predicts that plots of $1/(k^{corr} - k_0)$ *vs.* $1/[Im]_{free}$ should be linear, where k_0 is the rate constant for hydrolysis in the absence of buffer.[4] These plots are distinctly curved (Figure 2). (2) If significant quantities of $T^{\pm}$ were formed one should be able to observe such an intermediate spectrally. We expect that this intermediate would absorb at *ca.* 400 nm similar to *p*-nitroaniline. At concentrations of imidazole varying from 0.106 to 1.06 *M* (1:1 buffer and [I] = 2×10^{-4} *M*), the initial absorbance was identical for all solutions. These results rule out a rapid formation of intermediate in significant quantities. If one assumes an extinction coefficient of 2000 for the proposed intermediate, we estimate that we could easily have seen a 0.5% buildup.[5] (3) The reaction gives a good isobestic point at 355 nm, indicating that there is no *slow* buildup of intermediate. Furthermore, there is no induction period in the kinetics.

We would like to suggest that the results for the other ring-substituted trifluoroacetanilides are best interrupted by a mechanism involving general acid-catalyzed breakdown of a tetrahedral intermediate (Scheme I) and not nucleophilic catalysis. The observed rates can be adequately accounted for in terms of this mechanism (Table I and Figure 3)[7] but this fact in itself is not enough to allow a choice to be made between the two alternatives. At this point it is necessary to consider the original arguments used to reject the specific base-general acid mechanism and to propose a nucleophilic mechanism. It was stated[4] that a specific base-general acid mechanism was inconsistent with the kinetic results since the observed rate constants exceed the calculated value for $k_1[OH^-]$. However, this inconsistency is easily resolved by the inclusion of a general base term in the addition step ($k_1'[Im]$). At high concentrations of imidaz-

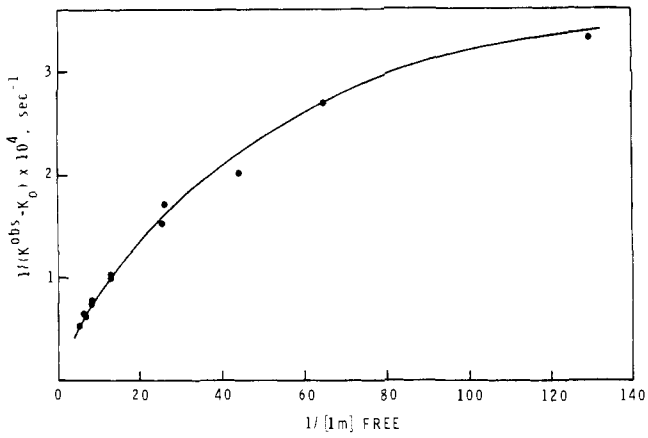


Figure 2. Plot of $1/(k^{obsd} - k_0)$ *vs.* $1/[Im]_{free}$ for the hydrolysis of *p*-nitrotrifluoroacetanilide at pH 7.06 and 25.0°. k_0 was calculated from the data of ref 3a.

Table I. Rate Constants for Imidazole-Catalyzed Hydrolysis of Ring-Substituted Trifluoroacetanilide at 30.0°

Substituent	k_1', M^{-1} sec^{-1} [a]	k_2'/k_{-1}[a]	Ref
p-NO_2	89.0×10^{-5}	200	*e*
m-Cl	13.5×10^{-5}	*d*	*f*
p-Cl	7.5×10^{-5}	350	*f*
m-OCH_3	7.9×10^{-5}	*d*	*f*
p-F	4.0×10^{-5}	*d*	*f*
H	3.3×10^{-5}	150	*f*
m-CH_3	2.5×10^{-5}	360	*f*
p-CH_3	4.3×10^{-5}	*d*	*f*
p-OCH_3	1.8×10^{-5}	170	*f*
p-NO_2[b]	35.0×10^{-5}	275	*e*
H[b]	0.75×10^{-5}	500	*f*
H[c]	2.0×10^{-5}	260	*f*

[a] We estimate errors of about 20 to 50% in these values. [b] D_2O. [c] *N*-Methylimidazole. [d] Could not be determined from the data. [e] This work (25.0°). [f] Calculated using data supplied to us by Dr. C. E. Stauffer (ref 4).

ole the rate is not limited by $k_1[OH^-]$ since the addition step is general base catalyzed.

Of more importance is the fact that the rate constants for these hydrolyses seem to follow a hyperbolic dependence on imidazole concentration. The linearity of double reciprocal plots of $1/(k^{obsd} - k_0)$ *vs.* 1/[imidazole] was used to support this contention.[4] However, the k_0 values obtained by this analysis are about ten times higher than the *actual* measured rate constants in the absence of buffer. For example, k_0 calculated on the basis of the nucleophilic mechanism for the trifluoroacetanilide at pH 6.87 is 2.12×10^{-4} min^{-1}. The actual rate constant in the absence of buffer, however, is 6.7×10^{-6} min^{-1}.[8] If the correct values for k_0 are used the plots which are generated are markedly nonlinear. Consequently, the observed kinetics are *not* consistent with the proposed nucleophilic mechanism.

The other major piece of evidence for the nucleophilic mechanism was the spectral observation of an intermediate at 260 nm (an initial absorbance increase over several minutes followed by a slower decrease).[4] We have attempted to reproduce this spectral change for trifluoroacetanilide and *m*-methoxytrifluoroacetanilide under a variety of conditions but we were unable to do so.[9] Only a decrease in absorbance corresponding to the hydrolysis reaction could be detected (Figure 4).[10]

In summary, we conclude that there is *no* evidence for either nucleophilic attack or formation of large quantities of an intermediate in these reactions.[11]

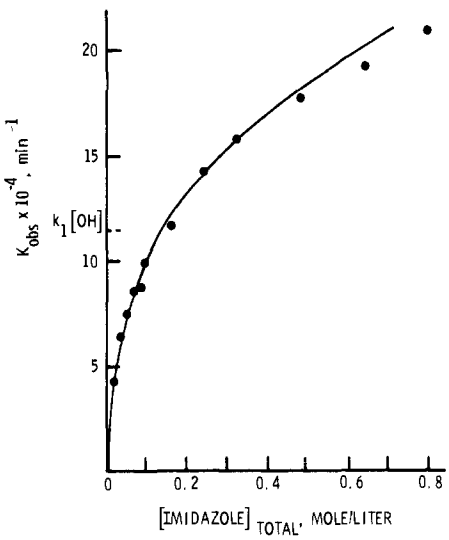


Figure 3. Plot of log *k* for the hydrolysis of trifluoroacetanilide *vs.* concentration of imidazole at pH 7.65 and 30° from ref 4. The line is the theoretical curve from eq 2 using the parameters in Table I (this work).

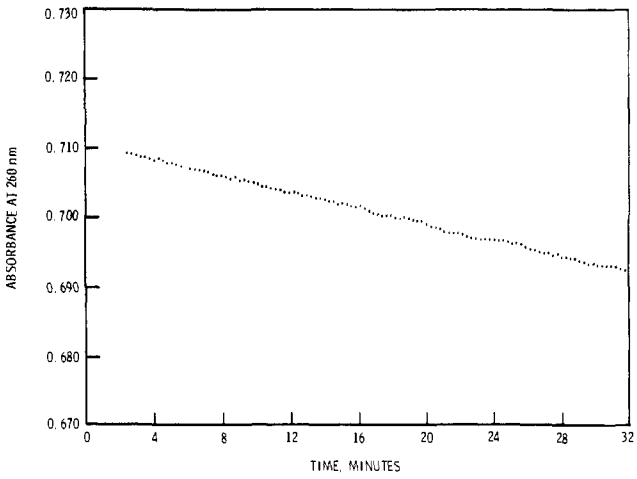


Figure 4. Change in absorbance at 260 nm for *ca.* 10^{-4} *M* trifluoroacetanilide in imidazole buffer at 25.0°. [Im] = 0.478, [ImH^+] = 0.500.

Experimental Section

Materials. Acylation of *p*-nitroaniline with trifluoracetic anhydride following the procedure of Bourne, *et al.*,[13] gave *p*-nitrotrifluoroacetanilide, mp 151.5–152.5 (lit.[13] mp 151.5–153). Distilled water was used for all kinetic runs. Imidazole was reagent grade and used either without purification or after recrystallization from chloroform. No differences were noted depending on whether the imidazole was recrystallized or not. Both batches were used in the search for an initial spectral change. The ionic strength was maintained with reagent grade sodium chloride.

D_2O solutions were made up using 99.8% D_2O and 1.0 *N* DCl in D_2O. At all concentrations of imidazole, the per cent D was 95% or better.

Kinetic Procedures. For spectral measurements, a stock solution of anilide in DMSO ($\sim 10^{-1}$ *M*) was prepared. About 3 ml of this stock solution was added to 3 cm^3 of buffer and the change in absorbance due to product nitroaniline was monitored at λ 400 nm as a function of time, using either a Cary 16K or a Gilford 2400 spectrophotometer. The temperature was kept at 25.0 ± 0.3° by circulating constant temperature water through the water-jacketed cell compartment of the spectrophotometer.

pH readings were taken on a Radiometer Model 26 pH before the kinetic measurements. Occasionally the pH of some of the dilute buffer solutions differed slightly from the concentrated ones.

When this occurred, the pH of the dilute solutions was adjusted using microliter amounts of 1 *N* NaOH or 1 *N* HCl. pH readings were generally taken after each run and agreement with the initial reading was usually ±0.03 pH units. Differences between pH readings of the buffer solutions used for a single-buffer plot were usually ±0.03. pD readings were taken as pH meter reading +0.4.[14]

Most reactions were followed through at least 3 half-lives and showed good first-order behavior. Rate constants for these reactions were calculated on a Wang 700 programmable computer using a nonlinear regression analysis program. For some of the slower reactions, the reaction was followed to about 2% completion and the rate constant was determined from the known value of the total absorbance change for the complete reaction.

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Supplementary Material Available. Data of imidazole-catalyzed hydrolysis of *p*-nitro-2,2,2-trifluoroacetanilide will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-75-377.

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(5) This estimate is probably conservative since the extinction coefficient of *p*-nitroaniline at 381 nm is 13,500.[6]
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(7) For all anilides, a plot of Stauffer's data shows a deviation from our theoretical curve at high concentrations of imidazole. In all cases, however, this deviation is small (less than 30%) and the experimental rate is slower than predicted. We attribute this result to a solvent effect; at 1.0 *M* imidazole, there is almost 7% organic component in the medium. In order to test this hypothesis, we examined the hydrolysis of *m*-methoxytrifluoroacetanilide at $[ImH^+] = 0.2$ *M* both in the presence and absence of 5% added dioxane. The solution with dioxane gave a rate constant 30% slower than the solution without dioxane.
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(9) We used samples of both these anilides supplied to us by Stauffer as well as a sample of trifluoroacetanilide synthesized by us.
(10) Our rate constants for the hydrolysis reaction agree well with those obtained by Stauffer.[4]
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Bis Annelations *via* 6-Methyl-2-vinylpyridine.[1a-c] An Efficient Synthesis of *dl-D*-Homoestrone

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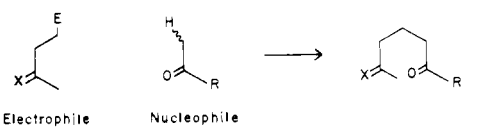
Abstract: The synthetic equivalence of 6-methyl-2-vinylpyridine with 3-vinylcyclohex-2-en-1-one has been demonstrated. The vinylpicoline is attached at the position α to a ketone by Michael addition. The cyclohex-2-en-1-one system bearing the substituent RCH_2 at the 3-position is elaborated from the 2-picoline bearing the substituent RCH_2 at the 6-position by a sequence involving metal–ammonia reduction, hydrolysis, and aldolization. An efficient conversion of the Wieland–Miescher ketone to *dl-D*-homoestrone, *via* this strategy is described.

The synthetic logic inherent in the methyl vinyl ketone (MVK) approach to the construction of cyclohexenones[2-4] has found extensive application in the synthesis of polycyclic natural products. While a wide assortment of variations has been introduced into the framework of this strategy, such annelations are characterized by two stages. The first involves the merger of an enolate (or enol) nucleophile with the electrophilic terminus (E) of an annelating agent. The agent is so constructed that the carbon-bearing function X is transformable to a ketone. In the final stage, a 1,5-hexanedione system undergoes intramolecular aldolization. In this cyclization, the nucleophilic enolate (or enol) is derived from the annelating agent, while the receptor carbonyl group arises from what was originally the nucleophile.

The modifications have dealt primarily with variations in the nature of the electrophilic terminus and with new methods for unraveling the 1,5-hexanedione required for cyclization. The researches of the Stork school[6a-d] have been particularly instrumental in expanding the feasibility of cyclohexenone annelations through a series of ingenious "oxobutyl" equivalents.



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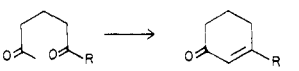
(2)

Another important advance in cyclohexenone syntheses arises from building into the annelating agent a substitution mode such that the α carbon of the enone, produced upon cyclization, emerges in a constructively functionalized form. The use of ethyl vinyl ketone,[4a,7,8] or its equivalent, in place of methyl vinyl ketone represents an example of this type of strategy. The Wenkert syntheses of the resin acids