J. Am. Chem. Soc. **1981**, *103*, 4874-4879

contain several minor impurities not easily removed by fractional distillation; it was purified by partial neutralization with HCl, removal of volatile material at reduced pressure, and recovery after basification much as described elsewhere[3] for the purification of piperidine; the distilled purified amine was shown by GLC to be of high purity. Butylmethylammonium chloride, mp 174-175 °C, was prepared by addition of 0.56 mol of HCl (as concentrated solution in water) to 0.64 mol of the amine, with stirring below 5 °C, cooling to −78 °C, collecting the crystalline salt, and recrystallizing from acetone. Anal. Calcd for $C_5H_{14}ClN$: Cl, 28.68. Found (by potentiometric titration): Cl, 28.64.

1-(Butylmethylamino)-2,4-dinitronaphthalene (**1c**) was prepared by the reaction of 1-chloro-2,4-dinitronaphthalene with a twofold excess of butylmethylamine in Me_2SO, and crystallized from ethanol; mp 69.5-70.5 °C. Anal. Calcd for $C_{15}H_{17}O_4N_3$: C, 59.40; H, 5.64; N, 13.85. Found: C, 59.60; H, 5.72; N, 13.91.

Spectral Characteristics and Changes. **1c** in Me_2SO shows a single broad absorption band with λ_{max} 425 nm, ϵ 7.80×10^3 M^{-1} cm^{-1}. Upon addition of butylmethylamine (0.875 M), the spectrum changes to one of two bands with λ_{max} 391 and 522 nm and ϵ respectively 1.45×10^4 and 2.41×10^4 M^{-1} cm^{-1}. The latter spectrum, attributed to **3c**, was essentially fully developed after 5 h at ambient temperature.

1a in Me_2SO shows a single absorption band with λ_{max} 439 nm, ϵ 1.90 $\times$ 10^4 M^{-1} cm^{-1}. Upon addition of pyrrolidine, the spectrum changes to one of two bands with λ_{max} 400 and 523 nm. When this spectrum due to **3a** is fully developed, ϵ at 523 nm is 1.85×10^4 M^{-1} cm^{-1} in the absence of pyrrolidinium chloride and 2.16×10^4 M^{-1} cm^{-1} in the presence of this salt (0.0104 M).

1b in Me_2SO shows a single broad absorption band with λ_{max} 422 nm, ϵ 7.8×10^3 M^{-1} cm^{-1}. Upon addition of piperidine, the spectrum slowly changes to one with two bands, λ_{max} 392 and 524 nm, attributed to **3b**, but the data were not suitable for definitive evaluation of ϵ for **3b**.

Kinetic Procedure. Reaction rates were determined by photometric observation of the absorbance at ca. 523 nm of reacting solutions. Determinations were made with use of a Gilford 2000 automated kinetics spectrophotometer with thermostated cell compartment. Good first-order behavior was observed in all cases. Rate constants were reckoned by the Guggenheim method. All kinetic runs were performed in duplicate; the rate constants reported are means of concordant values. The pseudo-first-order rate constant is symbolized k_ψ in Tables I and II.

Acknowledgment. This research was supported in part by the National Science Foundation. Our work was facilitated by preliminary observations of Dr. Lewis A. Smith. We thank Mr. Noboru Tone of the Department of Synthetic Chemistry, Gunma University, for assistance with some experiments concerning the reaction of **1a** with pyrrolidine, and Professor C. F. Bernasconi for criticism of a draft of this paper.

Acid-Catalyzed Hydrolyses of Acylpyrroles and Acylindoles. Noninvolvement of Protonated Substrates

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Abstract: The acid hydrolyses of *N*-(trifluoroacetyl)pyrrole, -indole, and -tetrahydrocarbazole and of *N*-acetylindole exhibit rate maxima in H_2SO_4 (20-40 wt %, $-H_0$ = 1-2.5) that are not due to extensive substrate protonation. The reactions have very large w and ϕ values, suggesting that there is a large difference in hydration of the initial and transition states. *N*-(Trifluoroacetyl)pyrrole is hydrated in water, and this evidence and that of hydrogen solvent isotope and salt and acid effects show that acid-catalyzed breakdown of a *gem*-diol is rate limiting. Rate maxima in acid hydrolyses of other weakly basic substrates can be explained in these terms.

Amides derived from aliphatic amines are weak bases with pK_a $\simeq -2$, and their acid hydrolyses are believed to involve a preequilibrium proton transfer followed by addition of water.[2,3]

The hydration of simple amides is energetically unfavorable[4] but should be assisted by protonation of the amide. The amino group of a first formed *gem*-diol should be readily protonated so that rapid carbon-nitrogen scission should be the preferred path of breakdown of a tetrahedral intermediate formed by addition of water to the conjugate acid of the amide. (The breakdown of amide acetals has formal similarities to the conversion of a tetrahedral intermediate into products.)[5-7] Several features of the acid hydrolysis of amides are readily understandable in these terms, for example, the rate maxima in moderately concentrated acid,[2,3] the changes in the solvent kinetic hydrogen isotope effect with increasing acid concentration,[8] and the absence of oxygen exchange between amide and water.[9] The relation between rate and acid concentration can be explained qualitatively in terms of an increasing protonation of the amide and a decreasing water activity as the acidity of the solution is increased.

N-(Trifluoroacetyl)pyrrole (**1**, **1a**) is extensively hydrated in water,[10] but its hydrolysis, although much faster than that of most other amides, can readily be followed over a wide range of pH.[11] The hydration is too fast to be followed by UV spectrophotometry, but it is slow on the NMR time scale and signals of both the amide and its hydrate are observed in aqueous acetonitrile.[10] These signals disappear as pyrrole is formed by hydrolysis. The hydrolysis is catalyzed by acids and in this paper we discuss some unusual kinetic features of this reaction.

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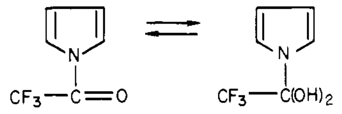
The acid hydrolysis of the chemically similar *N*-(trifluoroacetyl)indole and -tetrahydrocarbazole, **2** and **3**, respectively, and of *N*-acetylindole (**4**) have also been examined. Hydration of these compounds should also occur readily, although the equilibrium is in favor of the carbonyl species.[11]



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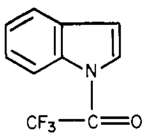

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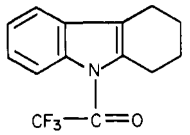

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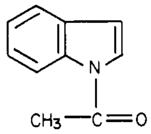

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The high reactivity of these *N*-acyl pyrroles and indoles is readily understandable[12,13] because the carbon–nitrogen conjugation is considerably reduced as compared with a simple amide. For example, the carbonyl stretching frequencies are 1730 and 1750 cm^{-1} for *N*-(trifluoroacetyl)pyrrole and -indole, respectively, and 1719 and 1720 cm^{-1} for *N*-acetylpyrrole and -indole, respectively, as compared with ~1600 cm^{-1} for aliphatic amides,[12] and the barriers for rotation about the amide bonds are much lower than for simple amides, e.g., *N,N*-dimethylacetamide.[14]

The observation of extensive hydration of **1** suggests that the role of the acid is to catalyze conversion of the *gem*-diol (**1a**) into products. There is precedence for this reaction path in hydrolyses of alkyl trifluoro- and trichloroacetate,[15,16] but so far as we are aware this system is the only one in which prior hydration has been demonstrated by physical methods.

Experimental Section

Materials. *N*-(Trifluoroacetyl)pyrrole. The potassium salt of pyrrole in dry Et_2O was added to a slight excess (15%) of $(CF_3CO)_2O$ in dry Et_2O under N_2. The mixture was vigorously stirred for 20 min and rapidly washed with aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), Et_2O was evaporated, and the residue was fractionally distilled. The fraction collected at 90–100 °C (yield 30%) was purified by preparative GLC (2 m, Silicone SE 30, 10% on Chromosorb at 50 °C); δ (MeCN) 7.45 (2 H, m, α-H) and 6.51 (2 H, m, β-H); $\nu_{C=O}$ 1730 cm^{-1}. The molecular weight (mass spectroscopy) and elemental analysis were those predicted for $C_6H_4NOF_3$. The low yield is due to polymerization and hydrolysis of the product in the workup with aqueous $NaHCO_3$.[11]

The preparation of the other reagents has been described.

Kinetics. Reactions were followed spectrophotometrically at 25.0 °C in aqueous acid at the following wavelengths: *N*-acetylindole, 236 nm; *N*-(trifluoroacetyl)pyrrole, 246 nm; *N*-(trifluoroacetyl)indole, 244 nm; *N*-(trifluoroacetyl)tetrahydrocarbazole, 260 nm. The substrate concentrations were in the range 10^{-4}–10^{-5} M. (It was necessary to use lower substrate concentrations in solutions of LiCl, which is strongly "salting out".)

The first-order rate constants, k_ψ (s^{-1}), were unaffected by changes in substrate concentration.

The reactions in the pH range were generally followed in solutions of HCl of the specified pH, and when [HCl] < 0.3 M was used, the ionic strength was brought to 0.3 by addition of NaCl. The experiments in HCl–LiCl mixtures were made in solutions of the pH measured in the presence of added LiCl.

Sulfuric acid was used for the experiments in the more concentrated acid, and rates in H_2SO_4 and D_2SO_4 were compared at the same mole fraction of acid.

Catalysis of phosphate or chloroacetate buffer was examined at a fixed pH at constant ionic strength (NaCl), using mixtures of acid and sodium salt.

Substrate Hydration. Formation of a *gem*-diol was detected only with *N*-(trifluoroacetyl)pyrrole (**1**). We measured the immediate decrease of absorbance at 246 nm when a solution of the pyrrole in MeCN (10 μL) was added to 2 mL of 0.1 M HCl. This rapid initial decrease of absorbance was followed by a slower decrease due to hydrolysis of the substrate. In estimating the extent of hydration we assumed that the extinction coefficient of **1** was the same in MeCN and H_2O.

Table I. Solvent Hydrogen Isotope Effects[a]

		substrate		
pH (pD)	D_2SO_4, wt %	*N*-acetylindole	*N*-(trifluoroacetyl)indole	*N*-(trifluoroacetyl)pyrrole
2.0			0.55 (3.5)	
1.9			0.80 (3.2)	
1.5			1.31 (2.4)	
1.0			3.68 (2.2)	
0.5			11.0 (2.3)	
	8			63.0 (2.7)
	20		50.3 (1.9)	
	30			446 (2.2)
	42	1.04 (2.2)	13.1 (1.8)	
	48	1.00 (2.4)	8.00 (1.5)	

[a] At 25.0 °C, values of $10^4 k_\psi$ (s^{-1}) in D_2O with DCl or D_2SO_4. The values in parentheses are k_{H_2O}/k_{D_2O} outside the pH (pD) range, calculated by using the same mole fractions of D_2SO_4 (or H_2SO_4) to D_2O (or H_2O).

Table II. General Acid-Catalyzed Hydrolysis of *N*-(Trifluoroacetyl)pyrrole[a]

[buffer acid], M	H_3PO_4[b]	CH_2ClCO_2H[c]
0.00	8.20	2.66
0.05	1.75	3.02
0.10		3.82
0.20	30.0	4.92
0.30		5.79

[a] Values of $10^5 k_\psi$ (s^{-1}) at 25.0 °C, μ = 0.3 (NaCl). The pH in the unbuffered system was controlled with dilute HCl. [b] H_3PO_4/NaH_2PO_4, pH 2.20. [c] CH_2ClCO_2H/CH_2ClCO_2Na, pH 3.00.

Results

Hydrolysis of *N*-Trifluoroacetyl Derivatives. The hydrolyses are acid catalyzed (Figure 1), although non-acid-catalyzed reactions make a considerable contribution to hydrolysis of *N*-(trifluoroacetyl)tetrahydrocarbazole (**3**) at low pH (see Discussion).

In dilute HCl (in the pH region) the reactions are first order with respect to hydrogen ion, but there are rate maxima in moderately concentrated acid even though the substrates are not extensively protonated. (The pK_a value of indole is −3.5[18,19] and the *N*-trifluoroacetyl derivatives will be very much weaker bases.)

Hydrolysis of *N*-Acetylindole (4). The relation between rate and acidity in the hydrolysis of *N*-acetylindole (Figure 1) is at first sight typical of acid hydrolyses of simple amides,[2,3] but this substrate is also too weakly basic to be extensively protonated in the reaction conditions.[18,19]

N-Acetylindole is considerably less reactive than *N*-(trifluoroacetyl)indole in aqueous acid (Figure 1). This electronic effect is that expected for nucleophilic addition to an unprotonated substrate, and electronic effects are generally small for bimolecular acid-catalyzed hydrolyses of more basic substrates, such as alkyl benzoates, which react by the $A_{Ac}2$ mechanism with attack of water on the conjugate acid.[20,21] Thus it appears that at least the *N*-(trifluoroacetyl)pyrrole and -indole react by a mechanism that does not involve water attack upon protonated substrate and

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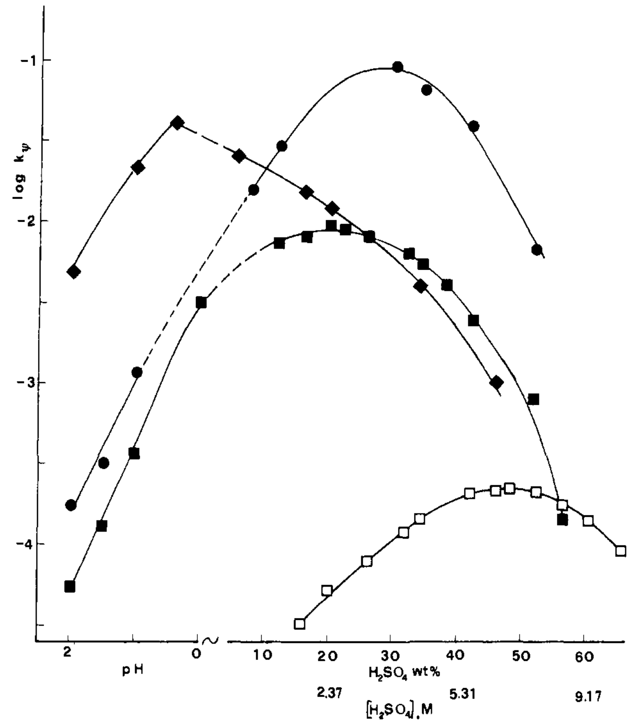


Figure 1. Acid hydrolyses of (□) *N*-acetylindole, (●) *N*-(trifluoroacetyl)pyrrole, (■) *N*-(trifluoroacetyl)indole, and (◆) *N*-(trifluoroacetyl)tetrahydrocarbazole.

that is different from that of the usual A2 deacylations.

Hydrogen Solvent Isotope Effects. Normal solvent hydrogen kinetic isotope effects are observed over a wide range of acidity (Table I). For dilute acid the isotope effect, k_{H_2O}/k_{D_2O}, was measured at given pH (pD) values by using HCl (DCl). For moderately concentrated acids molarity does not provide a useful measure of concentration, and therefore the isotope effects were compared by using solutions that contained the same mole fraction of H_2SO_4 (D_2SO_4), i.e., the same mole ratio of lyonium ion to H_2O (D_2O). These normal isotope effects are consistent with a slow proton transfer in the rate-limiting step. The changes in k_{H_2O}/k_{D_2O} are probably caused by a change from H_2O (D_2O) to very acidic media with a consequent change in the secondary solvent isotope effects.

General Acid Catalysis. Both chloroacetic and phosphoric acid catalyze hydrolysis of *N*-(trifluoroacetyl)pyrrole (Table II) as expected for a reaction involving a slow proton transfer.[22]

Effect of Lithium Chloride. Added lithium chloride decreases hydration of *N*-(trifluoroacetyl)pyrrole (Figure 2), and it also retards the acid-catalyzed hydrolysis of this substrate and the corresponding indole derivative. The negative kinetic salt effects are very similar for both substrates and the increase of acidity brought about by LiCl[23] is apparently not sufficient to offset the reduction in the amount of *gem*-diol and the reduced solvation of the transition state due to a decrease in water activity.[24]

Discussion

Rate-Limiting Step. Hydration can not be the rate-limiting step in the acid hydrolysis of *N*-(trifluoroacetyl)pyrrole, and the only reasonable role for the hydrogen ion is to assist carbon–nitrogen scission. The *gem*-diol of *N*-(trifluoroacetyl)pyrrole (**1a**) does not readily eliminate the anion of pyrrole,[10] and pyrrole and indole are very weak bases,[18,19] so that protonation of the pyrrole or indole moiety could be part of the rate-limiting step. (The values of pK_a for protonation of pyrrole and indole are -3.8 and -3.5, respectively, and indole is protonated on carbon at the 3 position.[18,19]

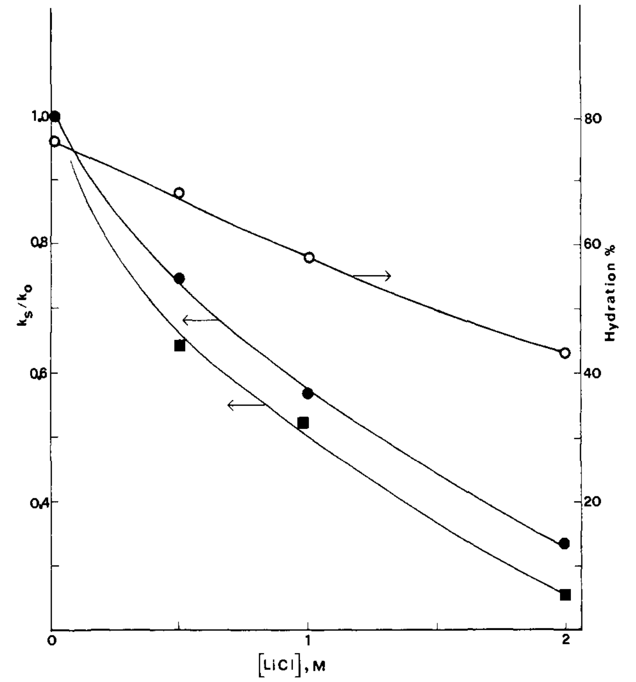
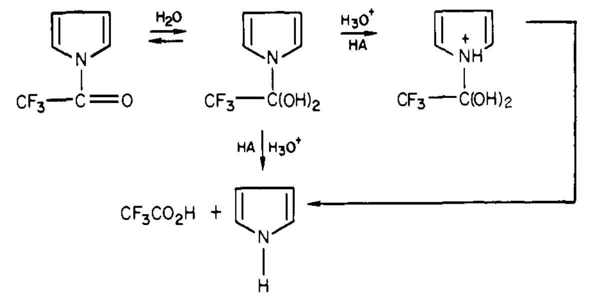


Figure 2. Negative salt effects upon hydration and hydrolysis in 0.1 M HCl: (○) hydration of *N*-(trifluoroacetyl)pyrrole. Solid points are rate constants relative to those in the absence of salts (k_s/k_0) for (●) *N*-(trifluoroacetyl)pyrrole and (■) *N*-(trifluoroacetyl)indole.

Scheme I



A reasonable mechanism of hydrolysis of **1** involving proton transfer to nitrogen is shown in Scheme I. The observation of general acid catalysis (Table II) is consistent with irreversible proton transfer to nitrogen (or carbon), preceding or being concerted with carbon–nitrogen scission.

Scheme I represents hydrolysis of *N*-(trifluoroacetyl)pyrrole, but similar mechanisms can be written for the other substrates. Because this mechanism involves attack of a hydrogen ion on a *gem*-diol, i.e., on the hydrate of the substrate, we designate it $S_E2(H)$. Both the negative salt effects and the rate maxima in aqueous acid can be related to electrolyte effects upon the activity of water,[24] which overcomes the electrolyte effects upon the protonating power of the hydrogen ion,[23] and added LiCl decreases the hydration of **1** (Figure 2). There also will be probable specific electrolyte effects upon the activity coefficients of the substrate and its *gem*-diol.[25] The substrates (**1**, **2**, **4**) show similar kinetics with regard to the dependence on acid and salt concentration (Figures 1 and 2) and the solvent hydrogen isotope effects (Table I), suggesting that they have similar mechanisms of hydrolysis, although only the *gem*-diol of *N*-(trifluoroacetyl)pyrrole was detected.[10] *N*-(trifluoroacetyl)pyrrole is more reactive than the indole derivative by ca. 1 order of magnitude (Figure 1), which is consistent with the extent of hydration of *N*-(trifluoroacetyl)indole being too low to be detected.

Relation between Reaction Rate and Acidity. Bimolecular hydronium ion catalyzed hydrolyses require involvement of hy-

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[22] Catalysis by weaker general acids could not be examined because of the incursion of a base-catalyzed hydrolysis at pH 3.[11]

[23] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

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[25] F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

Table III. Correlations of Reaction Rates with Acidity[a]

parameter	substrate *N*-acetylindole	 *N*-(trifluoroacetyl)indole	 *N*-(trifluoroacetyl)pyrrole
w^b	4.2 (6.2)	7.6 (10)	7.0 (10)
ϕ	0.8	1.6	1.7

[a] In H_2SO_4 at 25.0 °C, using H_0' values of C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Am. Chem. Soc.*, 91, 6654 (1969). [b] The values in parentheses were calculated in terms of the acidity function based on indole derivatives.[19,37]

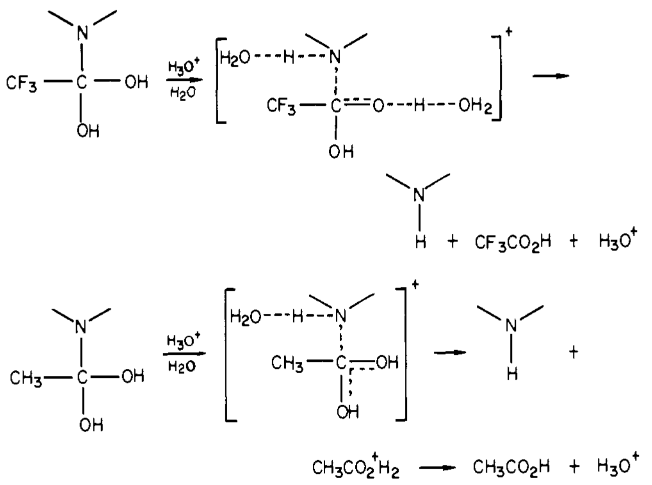
dronium ion and at least one water molecule acting as a nucleophile (other molecules can be solvating acidic centers or transferring protons). It is difficult to separate these functions of the medium because water is the strongest base present in appreciable concentration, and increases in acidity reduce the ability of water to react with an electrophile. However, many attempts have been made to devise a treatment that allows this separation.

In general, the protonating power of the medium is estimated in terms of an acidity function, e.g., Hammett's acidity function, H_0',[19,23] or a function that can be related to H_0' and the ability of water to act as a nucleophile or base is assumed to follow its activity as measured by its vapor pressure. One of the best known treatments is that of Bunnett,[26] although similar equations have been developed by others.[27] Bunnett's treatment, in its original form, involved plotting $\log k_\psi + H_0'$ against $\log a_{H_2O}$. The slopes, w, of these plots were believed to indicate the extent of involvement of water in the reaction,[28] and the relatively high w values (Table III) are indicative of a high dependence of the rate of hydrolysis of these acylpyrroles and -indoles on water activity. Other hydrolysis with similarly high w values are discussed.[15,16,30-36]

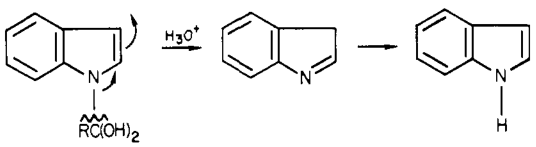
It is difficult, however, to distinguish between the roles of water as a nucleophile, a base, or a hydrogen-bond acceptor, and the problem is compounded by specific electrolyte effects of the acids[25] and questions regarding the choice of acidity function.[19,23] For example, we could use an acidity function based on protonation of indole in place of H_0'.[19,37] The corresponding Bunnett plots are linear, but the slopes are now considerably larger (Table III).

We found curved plots when we applied Bunnett's treatment to the acid hydrolysis of *N*-(trifluoroacetyl)tetrahydrocarbazole (**3**), possibly because of contributions from a non-acid-catalyzed reaction. It is important to note that Bunnett originally suggested that high w values indicated slow proton transfer in the rate-limiting step,[26] although he wrote his mechanisms in terms of a preequilibrium protonation of the substrate. Another analysis of the relation between rate and acidity was developed by Bunnett and Olsen, who found that plots of $\log k_\psi + H_0'$ against $H_0' + \log [H^+]$ were linear.[38] They correlated the slopes, ϕ, of these plots with w values and pointed out that this linear free-energy relationship gave information about the activity coefficients of the initial and transition states or, for an equilibrium, between the activity coefficients of the initial and final states. More recently, Modena, Scorrano, and their co-workers extended this treatment to provide evidence on the hydration requirements for acid-catalyzed reactions of the A1, A2, and S_E2 types,[39] avoiding the implication that w or similar parameters measure the number of water molecules directly involved in transition-state formation.

Scheme II



Scheme III



It was pointed out that this approach provided information on activity coefficient ratios by taking Hammett indicators as reference bases.[39]

Other treatments of hydrolysis in moderately concentrated acids have been developed, but they are based on the premise that an equilibrium proton transfer precedes attack of water.[27] Comparison of these treatments with that based on ϕ values is discussed in ref 39 and 40.

If we apply eq 1 to our results and include the logarithm of the water activity to take hydration of the carbonyl group into account, we obtain the predicted linear plots.

$$\log k_\psi + H_0' - \log a_{H_2O} = \phi(H_0' + \log [H^+]) + \log k_0 \qquad (1)$$

The values of ϕ are ~1.7 for hydrolyses of *N*-trifluoroacetyl substrates and 0.8 for hydrolysis of *N*-acetylindole (Table III). They accord with the other evidence which suggests that the transition states are very strongly hydrates. The ϕ value for hydrolysis of *N*-acetylindole is very similar to that of 0.7 for the acid hydrolysis of benzamide,[38] but the very low basicity of indole derivatives suggests that protonation is not the first step in the acid hydrolysis of *N*-acetylindole. (The normal solvent hydrogen isotope effects (Table I) support this conclusion.)[41]

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(31) C. A. Vernon, *Spec. Publ.-Chem. Soc.*, No. **8**, 17 (1957).

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(38) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, **44**, 1899, 1917 (1966).

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(40) Although the treatment based on ϕ values was initially formulated in terms of a preequilibrium proton transfer, it relates activity of coefficient ratios of transition state to substrate to those for protonation of a reference base, i.e., a Hammett indicator. The significance of the correlation therefore does not depend upon the timing of the proton transfer and water addition.

(41) A value of ϕ of 1.6 for the acid hydrolysis of *N*-(trifluoroacetyl)indole in D_2SO_4 can also be calculated by using the limited number of data points (Table I) and the values of Hammett's acidity function[42] and the activity of D_2O in D_2SO_4.[43] This value is identical with that in H_2SO_4 within the uncertainty of the calculation.

(42) E. Högfeldt and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960).

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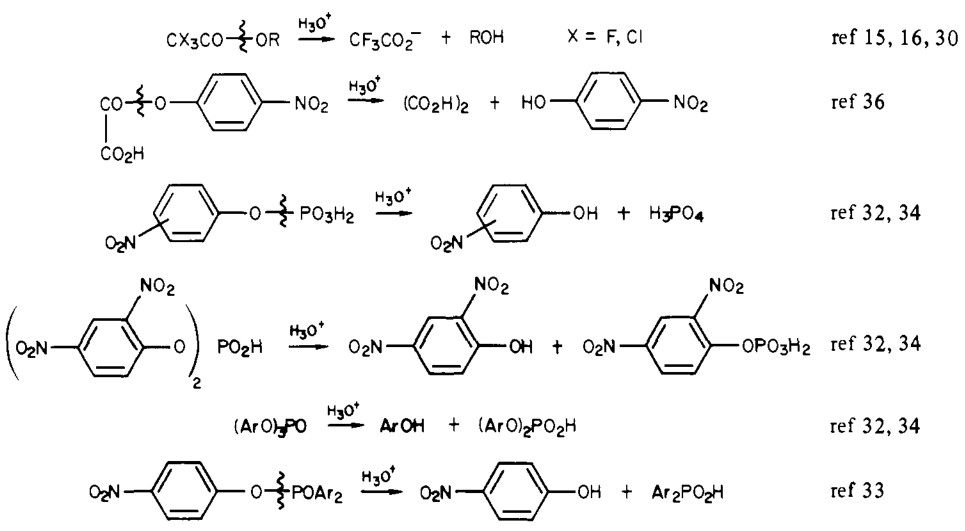
Scheme IV



The smaller values of *w* and *ϕ* for hydrolysis of *N*-acetylindole can be rationalized in terms of the basicity of acetic acid relative to trifluoroacetic acid.[44] Our assumed mechanism involves protonation of the indole or pyrrole moiety in the rate-limiting step of the reaction. This proton transfer may be concerted with, or precede, carbon–nitrogen scission and expulsion of the carboxylic acid and a hydrogen ion. The very high free energy of $CF_3CO_2H_2^+$ makes this ion an improbable intermediate, and water molecules will be required to deprotonate it in the rate-limiting step and so avoid formation of such a high-energy species.

On the other hand this deprotonation should be less important in the hydrolysis of *N*-acetylindole (**4**) where $CH_3CO_2H_2^+$ would be a reasonable intermediate. These differences are illustrated in Scheme II.

These reactions are shown as involving proton transfer to nitrogen but they could just as well involve protonation at carbon followed by a prototropic rearrangement (Scheme III) (cf. ref 18 and 37).

In principle the position of protonation could be distinguished by isotopic labeling, although concomitant C protonation of indole, for example, will complicate the analysis.

Small primary hydrogen isotope effects are often found when a proton is transferred between electronegative atoms as part of a rate-limiting step that involves reorganization of heavy atoms. This concept is exemplified by the solvation rule,[46] which suggests that only small primary isotope effects would be observed if decomposition of the *gem*-diol involved proton transfer to nitrogen, e.g., Schemes I and II. The observation of normal isotope effects in the hydrolysis of *N*-(trifluoroacetyl)indole (Table I) favors carbon protonation in the rate-limiting step (Scheme III), although the evidence is insufficient to exclude the possibility of nitrogen protonation.

Relation to Other Acid-Catalyzed Hydrolyses. It is usual for acid-catalyzed bimolecular hydrolysis to show rate maxima with increasing concentration of strong acid. For example, they are observed in deacylations of simple aliphatic esters and amides but only at acid concentrations in which the substrates are extensively protonated,[18,27,45] and they have been interpreted in terms of the slowing of nucleophilic attack on the protonated substrate with a decrease in water activity. They are not observed in A1 ester hydrolyses, which involve spontaneous breakdown of a protonated substrate.[30]

The rate maxima that we observe are superficially similar to those found in acid hydrolyses of aliphatic amides, but they and the hydrolyses of other weakly basic substrates (Scheme IV) have different origins.[15,16,30-36] There are also certain common features for hydrolysis of all the weakly basic substrates that show rate maxima in their acid hydrolyses. In all cases the substrates contain strongly electron-attracting groups, in the leaving group or bound to the reaction center, and for several of the reactions the solvent isotope effects, k_{H_2O}/k_{D_2O}, are normal or close to unity, whereas inverse isotope effects are characteristic of A1 and A2 hydrolyses.[47]

Kinetic studies and oxygen exchange show that the first step of hydrolysis of ethyl trichloroacetate involves water addition and that the hydrate can revert to reactant or go forward to products, and effects of acid catalysis on these steps have been studied.[16] The hydrolysis of ethyl trifluoroacetate also follows this general scheme.[15]

Various acid hydrolyses that we suggest do not involve attack of water upon protonated substrate are collected in Scheme IV.

Typical features of these acid-catalyzed reactions are that they involve attack of water on a strongly electrophilic centre and that they have large negative entropies of activation,[16] suggesting that several water molecules are involved in transition-state formation (cf. ref 26). The large negative electrolyte effects are also consistent with this involvement of water molecules and in some cases the rate maxima can be eliminated by using mixtures of HCl and LiCl of constant water activity.[34]

The acid hydrolyses of *N*-(trifluoroacetyl)pyrrole, -indole, and -tetrahydrocarbazole and *N*-acetylindole fit very clearly into the patterns illustrated by the reactions of Scheme IV. Addition of water should occur very readily because of the presence of strongly electron attracting groups, so that conversion of a *gem*-diol or similar intermediate into products is a key free-energy barrier to reaction.

Extensive oxygen exchange is observed in some but not all of the hydrolyses shown in Scheme IV. This failure to observe oxygen exchange does not rule out formation of a transient tetrahedral intermediate; it may mean that its life is too short for proton transfer to permit oxygen equilibration. For example, in dephosphorylation the requirement that a pentacovalent intermediate breakdown preferentially by loss of an apical group means that oxygen exchange between phosphate ester and water will not be observed unless the intermediate has a lifetime sufficient for pseudorotation to occur.[35,48]

Comparison of the "normal" reactions, where maxima in acid can be related to extensive protonation of the substrate,[2,3,45] with

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(44) The pK_a value of protonated acetic acid is ~−6, but trifluoroacetic acid is not protonated in 100% sulfuric acid so that it must be less basic than acetic acid by many orders of magnitude.[45]

(45) A. J. Kirby in ref 3, Chapter 2.

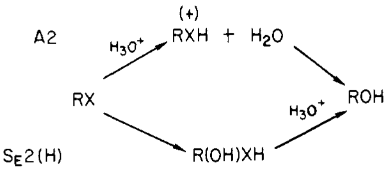
(46) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, **87**, 1553 (1965).

(47) In some cases there is concomitant spontaneous hydrolysis, which is inhibited by added electrolytes and by a decrease in the water content of the solvent. It is then possible that the rate maxima are due to inhibition of the spontaneous hydrolyses by the acid acting as an electrolyte. But this explanation cannot be applied to all examples of such rate maxima.

(48) E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3432 (1966).

J. Am. Chem. Soc. **1981**, *103*, 4879–4883

Scheme V



those of the weakly basic substrates discussed shows that relatively small changes in structure can lead to major changes in the kinetics form of the reaction in acid solution.

Relation between A2 and $S_E2(H)$ Mechanisms. The generally accepted A2 mechanism provides a reasonable model for many acid-catalyzed bimolecular hydrolyses,[20] but it fails for acid reactions of *N*-acylpyrroles and -indoles and probably for most of the reactions in Scheme IV. The mechanistic distinction depends on the timing of the addition of the hydrogen ion and water, and there should be a merging of the two mechanisms as the properties of the substrate change, e.g., going from a relatively basic amide to a readily hydrated acylpyrrole changes to mechanism from A2 (initial protonation) to $S_E2(H)$ (initial hydration).

For acid-catalyzed hydrolyses of a substrate, RX, the A2 and $S_E2(H)$ mechanisms can be represented as in Scheme V.

These reactions are drawn as stepwise processes, and it is reasonable that a relatively basic substrate should require activation to water attack by prior protonation, whereas the presence of strongly electron-withdrawing groups should favor hydration and require acid catalysis of conversion of the *gem*-diol into products.

Jencks[49] has discussed the relation between stepwise and concerted reactions and has pointed out that the latter avoid formation of high-energy intermediates, which is kinetically unfavorable.

These observations also suggest that it may be useful to reconsider bimolecular acid-catalyzed hydrolyses in terms of a spectrum of mechanisms depending on the timing of the various steps.

For example, acid hydrolyses or simple monoalkyl phosphates[35,50] have the kinetic form typical of water attack upon protonated substrate, whereas the acid hydrolyses of several aryl phosphates are relatively rapid but show rate maxima in acid. These "anomalous" hydrolyses have very negative entropies of activation and negative kinetics salt effects and show strong dependence on water activity. In addition, triaryl phosphates are very weak bases, so that their conjugate acids will be high-energy intermediates, which immediately suggests that hydrolysis will occur by a reaction path that avoids their formation. Thus there appear to be close similarities between these acid hydrolyses and those of the acyl pyrroles and indoles.

Hydrolyses of aryloxyphosphonium salts (**6**) can be regarded as models for attack of water upon a hypothetical protonated aryl phosphate (**7**).

$MeP(OAr)^{3+}$ **6** $(ArO)_3POH^+$ **7**

It is, however, difficult to reconcile the rate of hydrolysis of **6** with those of the acid hydrolyses of triaryl phosphates in terms of reaction between water and protonated substrate (**7**). But hydrolysis of **6** will be an inadequate model if acid hydrolysis of aryl phosphates does not occur by water attack upon protonated substrate.

For the acid hydrolysis of *N*-(trifluoroacetyl)pyrrole, the amide is in equilibrium with the *gem*-diol, and this is probably also true for hydrolyses of **2**–**4**. However, this is not the situation for several of the reactions shown in Scheme IV, if only because oxygen exchange between water and substrate is not observed, but the common feature is that they probably do not involve attack of water upon the protonated substrate even though this is the mechanism for hydrolysis of structurally similar but more basic substrates. In the acid hydrolysis of *N*-(trifluoroacetyl)pyrrole, the *gem*-diol is a low-energy species and its acid decomposition is rate limiting. For a simple aliphatic amide the conjugate acid is a low-energy species and its conversion to products with attack of water is rate limiting. Thus, with a systematic change of structure of an amide, it should be possible to change from one mechanism to another, possibly by reactions that involve concerted addition of water and proton transfer to the leaving group, and this possibility is being tested.

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Tridentate to Bidentate in a Platinum(II) Chelate: A 90° Anthranilaldehyde Rotation

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Abstract: The labilization of a coordinated formyl group in a platinum(II) chelate by nucleophilic ligands has been examined structurally. The chelating ligand is the deprotonated dimeric Schiff base condensate of *o*-aminobenzaldehyde. The aldehyde was trapped in its uncoordinated form by adding a 1:1 molar ratio of triphenylphosphine to the complex in acetonitrile. The resulting adduct crystallizes in the space group $C2/c$ with unit cell dimensions a = 32.75 (6) Å, b = 10.04 (2) Å, c = 19.71 (7) Å, and β = 118.5 (2)°. The immediate coordination sphere of the platinum consists of two nitrogens from the chelate, the phosphorus of the triphenylphosphine, and a chloride. The benzaldehyde ring, upon dissociation of the aldehyde oxygen from the platinum, has rotated 90° to a position perpendicular to the deprotonated *o*-aminobenzylidene group. The aldehyde oxygen is poised almost directly above the imine nitrogen at a distance of 2.87 (1) Å.

Introduction

The utility of transition metal ions in facilitating condensation reactions of organic substrates, particularly in the synthesis of macrocyclic ligands, is well documented. Unfortunately, the mechanistic details of many of these template reactions have been elusive. In order to elucidate mechanistic pathways and ultimately the role of the metal ion in these reactions, it is vital that the presence of postulated intermediates be verified. Many of the condensation reactions employed to yield macrocyclic products are of the Schiff base variety: the condensation of a carbonyl with

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