^{1}H NMR spectra. The carbonyl shifts in the isoelectronic analogues are also in the same direction; viz., the *E* acyl groups correspond to the downfield carbonyl resonances. However, the acetyl methyl (and propionyl methylene) shifts in the ^{13}C NMR spectra are different in the two systems. In the imide system proximity to the oxygen of the other carbonyl (i.e., the *E* configuration) is associated with a downfield shift while in the enolate system an upfield shift is observed.

The differences between these two isoelectronic systems as well as the differences between the assignments made here and those which have been made for simple *N,N*-dialkyl amides illustrate the difficulty in making a priori predictions and in extrapolating from one system to another, especially when the origin of the relative shifts is not well understood.

Experimental Section

Low-temperature (ca. −90 °C) ^{1}H NMR spectra were measured at 60 MHz on a Varian A60-A spectrometer equipped with a V-6040 variable-temperature controller. Low-temperature (ca. −90 °C) ^{13}C NMR spectra (except for that of **1**) were measured at 15.04 MHz on a JEOL FX-60 spectrometer with broad-band proton-noise decoupling. The NM 5471 variable-temperature controller was modified to use nitrogen gas which passed through coils cooled in liquid nitrogen. The ^{13}C NMR spectrum of **1** was measured at 25 MHz on a JEOL FX-100 spectrometer. Spectra were measured on 0.4 M solutions in 10-mm tubes. Diacetamide, acetylacetone, and hexane-2,4-dione were obtained commercially. *N*-Acetylpropionamide was prepared as described previously:[13] mp 85.5–86.5 °C (lit.[13] mp 86–87 °C). The sodium enolates were prepared by the dropwise addition of the β-diketone (11 mmol) in benzene or pentane to a benzene or pentane slurry of oil dispersed sodium hydride (0.547 g, 10 mmol, 57% oil dispersion). The mixture was stirred until the evolution of hydrogen gas ceased. The precipitate was filtered, washed with benzene, and dried in vacuo.

Registry No. 1, 625-77-4; 3, 19264-34-7; 4, 72844-58-7.

(13) Spotswood, T.; Polya, J. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 927.

Amine Catalysis of the Hydrolysis of Trifluoroacetanilide

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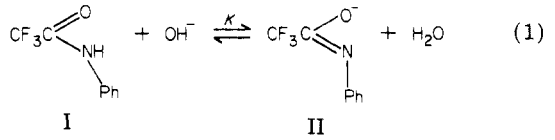
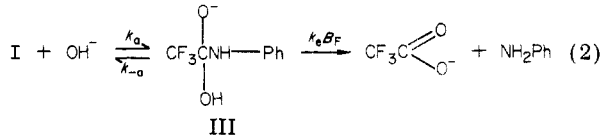
Only hydrolysis products could be isolated from the reaction of trifluoroacetanilide I with aqueous *n*-butylamine buffer at pH 10.5. Kinetic studies of the decomposition of trifluoroacetanilide I in aqueous morpholine, *n*-butylamine, piperidine, and trimethylamine buffers were also conducted. The most reasonable scheme for the reaction mechanism, compatible with all data, is presented in Scheme I and involves the general-base-catalyzed decomposition of the intermediate III which can be formed by hydroxide ion or water addition to I. Utilizing the constants of Table I, eq 6 is capable of predicting observed rate constants with an error of less than 9% (see Tables II and III). Some variation in values for these constants for trimethylamine buffers is observed and attributed to possible activity changes for the solutions. Deuterium isotope rate effects were determined for these constants in morpholine buffers. A value of $k_1^{H_2O}/k_1^{D_2O}$ of 0.39 was obtained and may indicate the presence of a third pathway for the generation of III (eq 9), involving the hydration of the anion II. A value of $k_4^{H_2O}/k_4^{D_2O}$ of 1.65 and a Brønsted β value of 0.23 for k_4 are interpreted to indicate general-base catalysis by the amine buffer. The low values for these quantities are indicative of a transition state involving an early proton transfer. General-base catalysis of proton transfer for the k_4 step is also indicated by the fact that trimethylamine appears to behave mechanistically, similar to the other amines used. The value of 8.8 obtained for $k_3^{H_2O}/k_3^{D_2O}$ clearly shows proton transfer to be occurring in this step as well. The results of this study thus support those suggested previously in that the hydrolysis of I undergoes a change in rate-determining step in mild alkaline aqueous solutions. This occurs because of the combination of the poor leaving ability of the anilinium ion and acyl activation present in the substrate trifluoroacetanilide.

2,2,2-Trifluoroacetanilide (I) is known to hydrolyze in mildly alkaline solutions.[1] The reaction is considerably faster than the alkaline hydrolysis of acyl-unactivated amides and appears to be catalyzed by a number of well-known general bases.[2-5] Acyl activation has not only increased the reactivity of this amide but has similarly affected its acidity; the probable pK_a being in the vicinity of 9.5 compared to "normal" values of approximately 15.[6] The mechanism of the reaction is believed to involve the general-base-catalyzed decomposition of a preformed tetrahedral intermediate (III) between the substrate and the hydroxide ion (eq 1 and 2).[2,3] Mader has suggested



(1)

I II



(2)

III

that II may hydrate to form III, but there is no evidence

(1) S. S. Biechler and R. W. Taft, *J. Am. Chem. Soc.*, **79**, 4927 (1957).
(2) P. M. Mader, *J. Am. Chem. Soc.*, **87**, 3191 (1965).
(3) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20**, 1892 (1966).
(4) S. O. Ericksson and L. Bratt, *Acta Chem. Scand.*, **21**, 1812 (1967).
(5) S. O. Ericksson, *Acta Chem. Scand.*, **22**, 892 (1968).
(6) A. G. Bruylants and F. Kezdy, *Rec. Chem. Prog.*, **21**, 213 (1960).

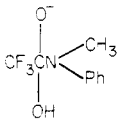
0022-3263/80/1945-2675$01.00/0

for it.[2] The base-catalyzed decomposition of III is not significantly faster than the return of III to starting material, and thus if the interpretation of the kinetic data is correct, this constitutes kinetic evidence for the existence of tetrahedral intermediates in the mechanism of amide hydrolysis. The conclusions reached in this study corroborate the above mechanism as most likely occurring when I disappears in aqueous solutions of pH above 9.5.

In 1965, Mader reported a kinetic study of this reaction in aqueous solutions containing up to 0.1 M hydroxide.[2] For solutions of low hydroxide concentration, he employed amine buffers. He found the rate of the reaction to be dependent on the buffer concentration but made no further attempt to investigate the nature of this dependence.

Eriksson et al. reported a kinetic study of the disappearance of I in a variety of aqueous buffered solutions.[3-5] These buffers include inorganic ions such as carbonate and phosphate species[3] as well as amines such as morpholine,[4] imidazole,[4] ethanolamine,[4] hydroxylamine,[5] hydrazine,[5] and ammonia.[4] Although the data from the inorganic buffers support the above mechanism, different kinetic terms were obtained for the amines. The new terms include general-acid catalysis of the breakdown of intermediate III by the protonated form of the buffer and basic self-catalysis of amide formation of the buffer. The latter term occurs in hydrazine and hydroxylamine buffers only.

Showen and Zuorick have reported that glycine, the glycinate anion, hydroxide, and water catalyze the disappearance of 2,2,2-trifluoro-*N*-methylacetanilide in aqueous solution.[7] They attribute this effect to the general-base-catalyzed decomposition of the intermediate IV. The



IV

apparent competition between the base-catalyzed decomposition of III and its return to starting material observed for I is no longer present.

This paper adds more extensive kinetic data on the rate of disappearance of I in aqueous amine buffers. The mechanistic scheme suggested, although similar to that of Eriksson, is more resonable and consistent with the extended data. In addition, product analysis and deuterium rate-effect data are reported.

Results and Discussion

The decomposition of 2,2,2-trifluoroacetanilide in 1.06 M *n*-butylamine buffer at pH 10.5 afforded 49% of aniline (isolated as the hydrochloride salt) and 80% of trifluoroacetate (isolated as the ammonium salt) as products. Kinetic studies of the decomposition of I in aqueous morpholine, *n*-butylamine, piperidine, or trimethylamine buffers were conducted under first-order conditions by using an ultraviolet spectrophotometer at 30 ± 0.3 °C. All the data obtained correlates well with the first-order kinetic equation (eq 3) to at least 3 half-lives.

$$-d[I]/dt = k_{obsd}[I] \quad (3)$$

Buffer dilutions were conducted at four different pH's with morpholine, two with *n*-butylamine, two with piperidine, and three with trimethylamine. Nine different rate constants were determined at each pH ranging from 0.01 to 1.0 M total buffer concentration. The basic form of the buffer ranged in concentration from 0.002 to 0.9 M. The ionic strength was maintained at 1.0 by the addition of potassium chloride.

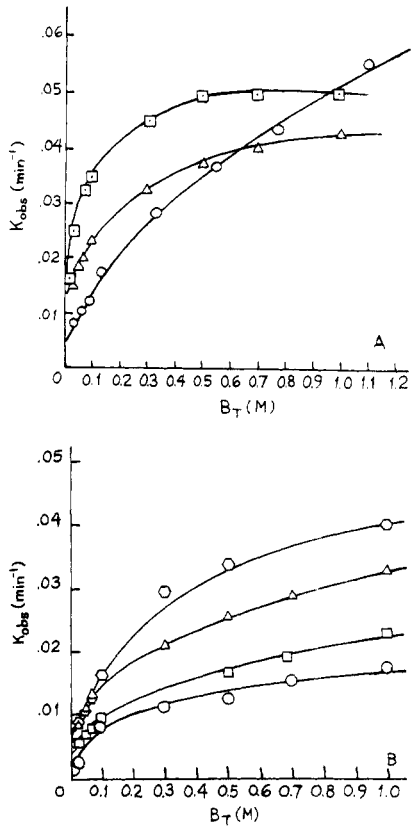


Figure 1. Plots of pseudo-first-order rate constants for the decomposition of trifluoroacetanilide vs. the concentration of total amine buffer, B_T, in aqueous solutions at 30 °C. Ionic strength was maintained at 1 by the addition of KCl. Part A: ○, trimethylamine, pH 10.07; △, *n*-butylamine, pH 11.13; □, piperidine, pH 11.72. Part B: morpholine, ○, pH 8.44; □, pH 8.83; △, pH 9.44; hexagons, pH 9.75.

All amines showed similar nonlinear dependence of the pseudo-first-order rate constants k_{obsd} on the concentration of the buffer. Rate profiles for some of the data are shown in Figure 1 (A and B). Figure 1B shows a family of curves obtained from the morpholine data.[8] They rise with the pH, indicating a dependence of the rate on the basic form of the buffer. The data collected for *n*-butylamine and piperidine are consistent with the mechanism of eq 1 and 2.[9] Equation 4 is derived from this mechanism by using

$$k_{obsd} = k_0 + \frac{k_a k_e B_F[OH^-]}{(k_{-a} + k_e B_F)(1 + K[OH^-])} \quad (4)$$

the steady-state approximation and can be used to predict the pseudo-first-order rate constants for these amines. In eq 4, k_0 represents the buffer-independent rate (i.e., the rate at zero buffer concentration) and B_F is the concen-

(7) R. L. Showen and G. W. Zuorick, *J. Am. Chem. Soc.*, 88, 1223 (1966); R. L. Showen, H. Jayaraman, and L. Kershner, *ibid.*, 88, 3373 (1966).

(8) The pseudo-first-order rate constants plotted for pH's 8.83 and 9.75 in Figure 1B are approximately twice the values plotted by Ericksson and Bratt.[4] No explanation is offered for this discrepancy. The methods used to collect these constants are considerably different in the two studies.

(9) See ref 4, p 1818, first paragraph. Although this author claims that amines with high pK_a's (such as *n*-butylamine) have little catalytic effect on the reaction, the data of this paper substantiates *n*-butylamine as behaving quite normally in relation to its pK_a.

Table I. Rate Constants Obtained by the Application of the Rate Data to Eq 4 or 6

amine	pK_a'[a]	k_a (k_1),[b] M^{-1} min^{-1}	k_e/k_{-a}(k_4/k_{-1})	$k_3k_2/(k_{-2} + k_3)$
morpholine	8.80	1643 ± 203	11.2 ± 3.3	0.0176
trimethylamine	10.02	2500 ± 330	5.3 ± 1.6	0.06
n-butylamine	10.56	1750 ± 213	10.9 ± 3.2	
piperidine	11.22	1880 ± 233	16.7 ± 5.0	
morpholine[c,d]	8.99	4200 ± 520	6.8 ± 2.0	0.002
k^{H_2O}/k^{D_2O} [e]		0.39	1.65	8.8

[a] Obtained by adding the log (B_F/B_{H^+}) to the pH determined for the buffered solutions. [b] Obtained as the slope of plots of $(1 + K[OH])/M$ vs. [OH] for each amine studied. [c] The solvent used was deuterium oxide. [d] For the deuterium oxide experiments, K was estimated as follows: K^{D_2O} = antilog ($pK_a^{H_2O} + 0.37 - pK_w^{D_2O}$) = 91 400. [e] Values obtained for the constants in aqueous morpholine buffers have been divided by the corresponding values obtained in deuterium oxide.

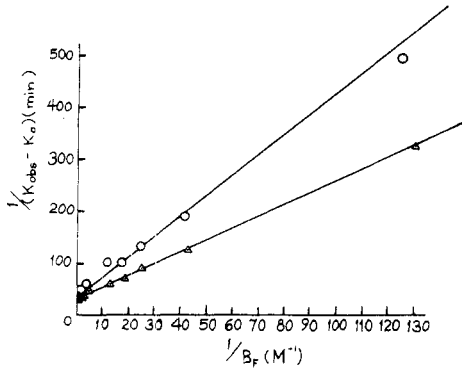


Figure 2. Plots of the reciprocal of the observed buffer-dependent rate of decomposition of trifluoroacetanilide vs. the reciprocal of the concentration of unprotonated buffer, $1/B_F$, for morpholine at pH 9.44, ○, and *N*-butylamine at pH 11.13, △.

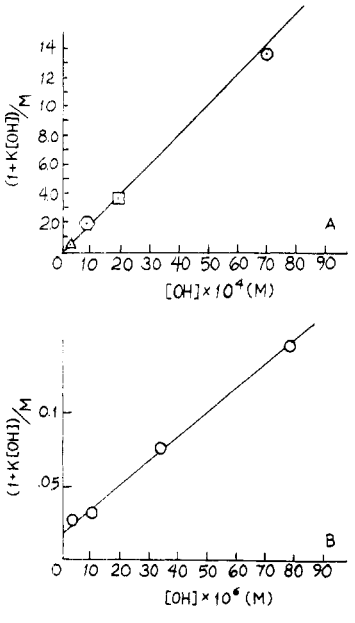
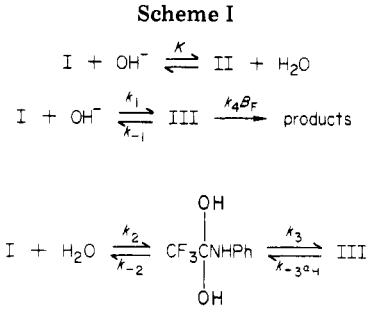


Figure 3. Plots of $(1 + K[OH])/M$ vs. the concentration of the hydroxide ion. Part A: for *N*-butylamine buffers at pH 11.13 (□) and pH 10.23 (△) and for piperidine buffers at pH 11.68 (○) and pH 10.80 (hexagons). Part B: for morpholine buffers at pH's 8.44, 8.83, 9.44, and 9.75.

tration of the basic form of the buffer. The values for k_a and the partition coefficient for the intermediate III, k_e/k_{-a}, listed in Table I are determined from plots of $1/(k_{obsd} - k_0)$ vs. $1/B_F$ at each pH. Figure 2 shows representative plots of this sort for *n*-butylamine and morpholine buffers. The intercept, M, of such a plot is given by $(1 + K[OH])/k_a[OH]$. Therefore, the relationship of eq 5 should hold. Figure 3A shows a plot of $(1 + K[OH])/M$ vs. [OH] for the data of these amines at each pH where data were collected. The slope of this plot gives a value of 1870 min^{-1} for k_a. The quantity k_e/k_a is equal to the intercept divided by the slope of the double recriprocal plot. The values reported in Table I are the averages of the values obtained for each pH.

Scheme I



$$(1 + K[OH])/M = k_a[OH] \quad (5)$$

Figure 3B shows a similar plot (i.e., similar to that of Figure 3A) for the data from four pH's with morpholine buffers. The slope gives a value of 1634 min^{-1} for k_a, in reasonable agreement with the slope of Figure 3A. However, as neutrality is approached, the rate does not reduce to zero as would be predicted by eq 4. It seems reasonable then to presume that at lower concentrations of hydroxide, as suggested by Mader, the intermediate III may also be formed by the ionization of hydrated I.[2] The mechanism thus becomes more complex and must now be represented by that of Scheme I. The observed pseudo-first-order constants are now obtained from eq 6 where a_H represents

$$k_{obsd} = k_0 + \frac{\left(\frac{k_3k_2}{(k_{-2} + k_3)} + k_1[OH^-]\right)k_4B_F}{(1 + K[OH^-])\left[k_{-1} + k_4B_F + k_{-3}a_H\left(1 - \frac{k_3}{k_{-2} + k_3}\right)\right]} \quad (6)$$

the activity of the hydrogen ion as measured by a glass electrode. The slope of Figure 3B is then represented by k_1 and the intercept by the hydration rate constants $k_3k_2/(k_{-2} + k_3)$.

The slope divided by the intercept of the double reciprocal plots (see Figure 2) is then given by eq 7. If k_{-2} is

$$\frac{\text{slope}}{\text{intercept}} = \frac{k_{-1}}{k_4} + \left[1 - \frac{k_3}{k_{-2} + k_3}\right]\frac{k_{-3}a_H}{k_4} \quad (7)$$

considered to be much smaller than k_3, k_4/k_{-1} may be calculated exactly as k_e/k_{-a} was for the data of *n*-butyl-

Table II. Comparison of Experimentally Determined and Calculated Pseudo-First-Order Rate Constants for *n*-Butylamine at pH 11.13

B_T,[b] M	k_{obsd}(exptl),[a] min^{-1}	k_{obsd}(calcd),[c] min^{-1}
0.01	0.0097	0.0097
0.03	0.0146	0.0146
0.05	0.0180	0.0184
0.07	0.0201	0.0214
0.1	0.0229	0.0248
0.3	0.0322	0.0353
0.5	0.0371	0.0390
0.7	0.0400	0.0409
1.0	0.0428	0.0425

[a] Reproducible to ± 8%. [b] Total concentration of both forms of the buffer. [c] Calculated with the aid of eq 4 and the appropriate values for the constants listed in Table I.

amine and piperidine. This seems a reasonable consideration since the removal of a proton ought to be easier than the hydration of the carbonyl group. The values obtained for k_4/k_{-1} in this fashion for each pH are constant within experimental error.

The data collected for the trimethylamine buffers at pH's 9.58, 10.07, and 10.52 are also consistent with Scheme I and eq 6. The numbers appearing in Table I for this amine were determined exactly as the corresponding values were obtained for morpholine.

Kinetic data were also collected for morpholine buffers at pD's 8.87 and 9.85 by using deuterium oxide as the solvent. The rate constants obtained and deuterium rate effects calculated for these constants also appear in Table I.

Table II affords an indication of the accuracy of eq 4 at predicting the pseudo-first-order rate constants obtained experimentally for *n*-butylamine buffers at pH 11.13. The error is less than 9% and is typical of all of the data collected.

The pH's employed for the *n*-butylamine and piperidine buffers were considerably higher than those for morpholine or trimethylamine. Under these conditions, the principal path for the generation of the intermediate III is by reaction of I with hydroxide. The uncatalyzed decomposition of III (represented by k_0) is of little significance and thus very difficult to measure accurately. The value of 1870 M^{-1} min^{-1} obtained for k_a is in good agreement with the value of 1877 M^{-1} min^{-1} reported by Mader.[2]

At pH's nearer to neutrality, the rate of reaction of I with hydroxide is moderated to the extent that its hydration becomes a significant path for the production of the intermediate III. Significant portions of the rate of hydrolysis of acyl halo esters as well as oxalates, carboxylic acid anhydrides, and lactones have been found to occur by initial hydration of the acyl-activated carbonyl substrate.[10,11] Acyl activation will apparently increase the rate at which the carbonyl of the substrate is saturated compared to the rate of the second or carbonyl regeneration step. This permits weaker bases such as water to become observable nucleophilic agents. For the morpholine buffers, the value of 1634 M^{-1} min^{-1} for k_1 is in adequate agreement with Mader's value, but the corresponding number for the trimethylamine buffers is somewhat high. It is conceivable that such concentrations of aqueous trimethylamine have undergone slight activity changes. This is borne out by the fact that the values for the other

(10) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 83, 1743 (1961).
(11) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. I, W. A. Benjamin, New York, 1966, Chapter 1.

Table III. Comparison of the Experimentally Determined and Calculated Pseudo-First-Order Rate Constants for Morpholine

pH	B_T, M	$k_{obsd} - k_0$ (calcd)[a]	B_F, M	$k_{obsd} - k_0$ (calcd)[b]	$k_{obsd} - k_0$ (exptl)
8.37	0.01	0.00575	0.0026	0.000577	0.00093
8.37	0.10	0.00458	0.026	0.00458	0.00740
8.37	1.00	0.0152	0.260	0.01512	0.0167
8.84	0.01	0.00126	0.005	0.000499	0.0016
8.84	0.10	0.00844	0.049	0.00420	0.0080
8.84	1.00	0.0201	0.487	0.01623	0.0214
9.40	0.01	0.00245	0.0079	0.000547	0.00205
9.40	0.10	0.0142	0.079	0.00470	0.01029
9.40	1.00	0.0267	0.788	0.01958	0.02962
9.71	0.01	0.00301	0.0089	0.000585	0.00260
9.71	0.10	0.0166	0.089	0.00504	0.0145
9.71	1.00	0.0303	0.885	0.0213	0.0379

[a] Calculated with the aid of eq 6 as written. [b] Calculated with the aid of eq 6 modified to include a term for a kinetic pathway represented by eq 8.

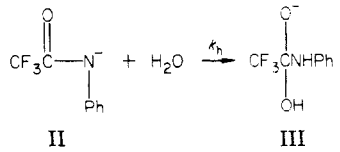
constants for trimethylamine in Table I are also somewhat inconsistent with the corresponding values for morpholine.

It has previously been stated that Scheme I requires a term involving general-acid-catalyzed decomposition of III by the protonated form of the morpholine buffer BH^+ as in eq 8.[4] Table III shows clearly that such a term is not

$$\text{III} \xrightarrow{k_5[BH^+]} \text{products} \qquad (8)$$

needed to explain the data reported in this paper. In column 3 and 5 are given the buffer-catalyzed pseudo-first-order rate constants as calculated first according to eq 6 and then according to eq 6 plus a term for general-acid catalysis as shown in eq 8. When these calculations are compared to the corresponding experimentally determined ones in column 6, it is readily apparent that eq 6 alone, and thus Scheme I, best explains the kinetic data. The value used for k_5/k_{-1} was obtained as the slope of a plot of (intercepts)$(K_a + a_H)$/(slopes) vs. a_H where K_a is the ionization constant for the morpholinium ion at 30 °C. The intercepts and slopes come from plots of the reciprocal of the buffer-catalyzed rate vs. the reciprocal of the total buffer concentration (i.e., $[B_F]$ and $[BH^+]$) at each given pH where buffer-dilution studies were conducted. Catalytic terms for HCO_3^-, $H_2PO_4^-$, HPO_4^{2-}, and OH^- were also obtained for the hydrolysis of I. The rate paths involving HCO_3^-, $H_2PO_4^-$, and HPO_4^{2-} were explained in terms of their ability to donate and accept a proton simultaneously in the transition state.[3] However, neither OH^- nor amines can perform this function, and thus it seems that general-base catalysis alone is the more consistent explanation.

The deuterium rate effect for k_1 as determined in the morpholine buffer is 0.39. This is surprising since according to the mechanism only secondary rate effects should be observable. Mader has suggested, in his hydrolysis mechanism, that III can arise by hydroxide attack on I or, alternatively, by hydration of the anion II.[2] These two pathways are kinetically indistinguishable, and thus both are not necessary to explain the data. However, if both pathways are operative, k_1 of Scheme I becomes $(k_1 + k_h'K)$ where $k_h'K$ represents the hydration pathway for the production of III from the anion II (eq 9). Under these



II III (9)

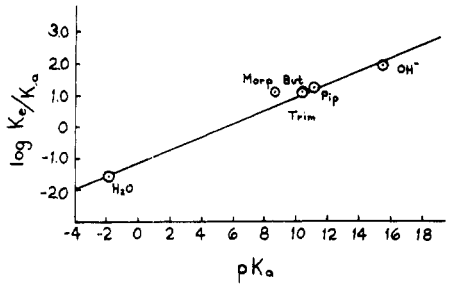


Figure 4. Brønsted plot for k_e/k_{-a} using the data from this study and some from the study of Eriksson and Holst.[3]

conditions the value of 0.39 obtained would reflect K^{H_2O}/K^{D_2O}. A value of $K^{H_2O}/K^{D_2O} = 43\,100/91\,400 = 0.47$ can be estimated for this quantity (see Table I, footnote *d*). The deuterium rate effect observed for k_1 thus supports Mader's contention indirectly.

The deuterium rate effect calculated for k_4/k_{-1} of 1.65 in Table I will reflect $k_4^{H_2O}/k_4^{D_2O}$ because $k_{-1}^{H_2O} \approx k_{-1}^{D_2O}$ since the k_1 path would also involve only secondary rate effects as a result of deuterium substitution. The value obtained does not discredit the probability that the pathway k_4 involves general-base catalysis of the decomposition of III by the unprotonated morpholine molecule.

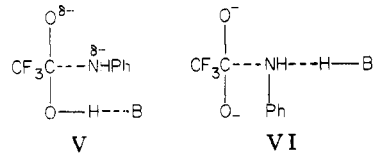
General-base catalysis of the decomposition of the intermediate III is also supported by the product-analysis data in *n*-butylamine buffers as well as by catalysis by trimethylamine, carbonate, and phosphate anions.[3] Since these latter bases are not known to produce stable intermediates by nucleophilic addition to the carbonyl of carboxylic acid derivatives as are primary and secondary amines, it is likely that all amines perform the same catalytic role.[12] Eriksson's data on hydroxylamine and hydrazine involving kinetic terms second order in amine may have little bearing on the mechanism involving other amines since they both have extraordinary reactivity due to α nonbonded pairs.[5]

Figure 4 shows a plot of log k_4/k_{-1}(log k_e/k_{-a}) vs. the pK_a's of the general bases used in this study as well as that of Eriksson and Holst.[3] According to the Brønsted catalysis law, eq 10, a straight line should be obtained.[13] The value of the slope, β, is indicative of the sensitivity of the

$$\log k = \beta pK_a + C \qquad (10)$$

rate constant to basic catalysis. A β value of 0.23 which was obtained from Figure 4 is low but still within the range of general-base catalysis.[11] Showen and Zuorick report a value of ~0.3 for β in their study of 2,2,2-trifluoro-*N*-methylanilide.[7]

A value of this magnitude for β is indicative of an easy proton transfer and thus provides support for an early transition state in the catalytic step.[11] Two kinetically indistinguishable transition states have been suggested by Showen and Zuorick in their study of 2,2,2-trifluoro-*N*-methylanilide and are depicted by V and VI for this study.[7]



Transition state VI follows a preequilibrium proton transfer from III to the general base. Whether V or VI is operative, it is obvious that bond breaking between the aniline leaving group and the carbonyl carbon must be well advanced in the transition state in order that proton transfer be from the weaker to the stronger base. The transfer of a proton from a stronger to a weaker base should have a β value greater than 0.5.

Support for an early transition state in the catalysis step for the reaction is also gained by the small deuterium isotope rate effect exhibited for k_4. The value of 8.8 reported in Table I represents $[(k_3k_2)/(k_{-2} + k_3)]^{H_2O}$ divided by the corresponding value obtained in deuterium oxide. Because no net oxygen to hydrogen bonds are broken in the hydration of the substrate, $k_2^{H_2O} \approx k_2^{D_2O}$ and $k_{-2}^{H_2O} \approx k_{-2}^{D_2O}$. The quantity 8.8 reflects mainly differences between $k_3^{H_2O}$ and $k_3^{D_2O}$ and clearly shows that this could involve the removal of a proton from the hydrated substrate.

The hydrolysis of 2,2,2-trifluoroacetanilide thus involves a change in rate-determining step under the conditions of this study because the combination of acyl activation and poor leaving ability of the anilinium ion allows comparable partitioning of the intermediate III. For esters this does not occur because of the increased ease of leaving ability possessed by the alkoxide anion. The acyl activation of esters does increase the rate of nucleophilic addition, but not sufficiently. *N*-Methylation of 2,2,2-trifluoroacetanilide apparently slows the rate of leaving, and thus the general-base-catalyzed loss of the *N*-methylanilinium ion becomes its rate-determining step.[7]

Experimental Section

Materials. The following amines, purchased from Eastman, were freshly distilled before use: morpholine (bp 120 °C), *n*-butylamine (bp 70 °C), and piperidine (bp 97 °C) (atmospheric pressure 596 mm). Eastman red- and white-label trimethylamine hydrochloride and Baker Analyzed potassium chloride were used as obtained.

Trifluoroacetanilide. Trifluoroacetic anhydride (2.1 g) and aniline (0.93 g) were dissolved and allowed to stand 30 min in 15 mL of acetonitrile at room temperature. The solvent was removed, leaving a solid crystalline residue which was recrystallized from an ethanol–water mixture. The air-dried gray needles obtained were sublimed at 100 °C (5 mm), affording 0.92 g (55%) of white plates, mp 86–88 °C (uncor) (lit. mp 84–85 °C).[1]

Apparatus. Spectrophotometric kinetic measurements were conducted with a Cary Model 15 ultraviolet spectrophotometer equipped with a Cary Model 1541 automatic sample changer. The sample cell was thermostated by circulated water at 30 ± 0.3 °C from a Precision Scientific Model 154 low-temperature temperature regulator. Measurements of the pH of the buffer solutions were conducted inside the temperature bath with a Sargent Model LS pH meter using a Sargent S-30070-10 miniature combination glass–calomel electrode. For reactions conducted in deuterium oxide, the pD was determined by adding 0.37 to the reading obtained for the glass electrode.[14]

Product Analysis. Reaction of Trifluoroacetanilide with Aqueous Buffered *n*-Butylamine. A modification of the method of Biechler and Taft was employed.[1] To 1.93 g of *n*-butylamine in 25 mL of aqueous solution containing 6.5 mL of 0.927 N hydrochloric acid (pH 10.5) was added 0.680 g of trifluoroacetanilide. The resulting mixture was allowed to stand overnight at room temperature.

The mixture was then adjusted to pH 6 with concentrated hydrochloric acid and extracted three times with ether. The ether extracts were combined and saturated with gaseous hydrogen chloride, affording 191 mg (49%) of an aniline hydrochloride (mp 192–194 °C) which was collected by suction and found to be identical with an authentic sample.

The original reaction solution was acidified with 7 mL of concentrated hydrochloric acid and extracted with three portions

(12) See ref 4, p 1819, paragraph two.
(13) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed., Wiley, New York, 1961, p 218.
(14) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, 65, 1079 (1961).

of ether. The ether extracts were combined, and the ether was removed by distillation. Concentrated aqueous ammonia (15 mL) was added to dissolve the small amount of liquid residue. The removal of liquid from the solution produced 317 mg (80%) of ammonium trifluoroacetate (mp 122–123 °C) which was dried 30 min at 100 °C under 5 mm of pressure and found to be identical with an authentic sample.

Kinetic Procedure. The concentrations of amine buffer in all solutions were maintained in large excess over that of trifluoroacetanilide in order to provide a strong buffering capacity. Except for trimethylamine, buffered solutions were prepared shortly before use by the addition of calculated amounts of standardized hydrochloric acid solution to weighed amounts of freshly distilled amine. For trimethylamine buffers, calculated amounts of standardized aqueous potassium hydroxide were added to aqueous solutions containing weighed amounts of trimethylamine hydrochloride. The water employed was doubly distilled from glass. A dilute solution of trifluoroacetanilide was prepared in ethanol. The reactions were initiated by addition of about 0.01 mL of trifluoroacetanilide solution to a cuvette containing 3 mL of amine buffer solution. The amine buffer had been previously thermostated in the Cary instrument and after momentary agitation was returned to that position where the disappearance of absorption at 262 nm was followed spectrophotometrically. Pseudo-first-order rate constants (k_{obsd}) were determined from the slopes of log $(A_0 - A_\infty)/(A_t - A_\infty)$ vs. time. All actual computations were carried out on an Olivetti-Underwood Programma 100 computer utilizing a weighted least-squares program written by Dr. Donald Tanner. Representative numbers of these computations were plotted to ensure that the reactions were indeed conducted under first-order conditions.

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Registry No. I, 404-24-0; trifluoroacetic anhydride, 407-25-0; aniline, 62-53-3; aniline hydrochloride, 142-04-1; ammonium trifluoroacetate, 3336-58-1; morpholine, 110-91-8; trimethylamine, 75-50-3; *n*-butylamine, 109-73-9; piperidine, 110-89-4.

Optical Rotatory Dispersion Studies. 130.[1] Additivity of Deuterium Octant Contributions in Cyclohexanone

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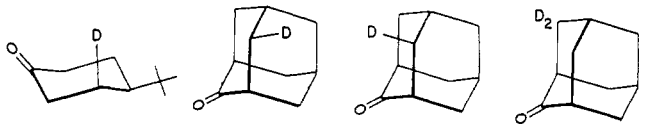
A comparison between the circular dichroism spectra of (4*S*)-3,3-dideuterio-4-methylcyclohexanone (1), (3*R*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (2), and (3*S*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (3) leads to the conclusion that the octant contributions of deuterium in the β-equatorial and β-axial positions of the cyclohexanone ring are additive. From the temperature-dependent circular dichroism spectra of 1 an energy difference of −1.1 kcal/mol was obtained for the conformations with the 4-methyl substituent in the axial and equatorial position, respectively.

The octant contributions of isotopes toward the rotational strength of the n → π* Cotton effect of ketones have formed the subject of several recent experimental studies.[2-5] From them a picture has emerged which permits accurate predictions of the rotational strength of such molecules by viewing the isotope as a perturber which has a certain (experimentally determined) group contribution in different locations of the molecule. This interpretation has been substantiated by recent CNDO/S calculations[5] which have previously[6] been shown to yield reliable rotational strengths for substituents such as the methyl group. In general the C–D bond has been found to make a dissignate contribution; i.e., it is a weaker perturber when compared to the C–H bond at the same or the mirror-image location of the octant diagram. In this publication we address ourselves to the question of additivity of contributions when more than one hydrogen is substituted by deuterium. As an example we have chosen to synthesize (4*S*)-3,3-dideuterio-4-methylcyclohexanone (1) (Scheme I).

The octant contributions for a β-equatorial and β-axial deuterium in the conformationally rigid cyclohexanones (3*R*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (2) (Scheme II) and (3*S*,4*R*)-3-deuterio-4-*tert*-butylcyclohexanone (3)



3 4 5 6

have been reported previously by us,[3] and we compare our results with those obtained for the corresponding adamantanones 4, 5, and 6 reported by Lightner[2] and Wynberg.[4] The synthesis of 2 was repeated via a different synthetic route which resulted in a more reliable determination of its enantiomeric excess. In addition, we report the synthesis of (4*S*)-2,2,3,3,4,6,6-heptadeuterio-4-methylcyclohexanone (7) (Scheme I), the perdeuterated analogue of 1, which can formally be considered to owe its chirality to the substitution of deuterium vs. hydrogen.

Synthesis

(4*S*)-3,3-Dideuterio-4-methylcyclohexanone (1) was synthesized from dihydrocarvone (8)[7] (containing 10–18% of the cis diastereomer) as outlined in Scheme I. Reduc-

(1) For preceding paper, see: Lee, S.-F.; Edgar, M. T.; Pak, C. S.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.*, in press.
(2) Lightner, D. A.; Chang, T. C.; Horwitz, J. *Tetrahedron Lett.* **1977**, 3019–3023; errata. *Ibid.* **1978**, 696.
(3) Sundararaman, P.; Djerassi, C. *Tetrahedron Lett.* **1978**, 2457–2460; errata. *Ibid.* **1979**, 4120.
(4) Numan, H.; Wynberg, H. *J. Org. Chem.* **1978**, *43*, 2232–2236.
(5) Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.*, **1980**, *102*, 1983–1990.
(6) Bouman, T. D.; Lightner, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 3145–3154.
(7) Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647–4648.

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