

A sample of **27** was treated with copper acetate solution to give the green copper chelate **29**, m.p. 138–139° after three recrystallizations from ethanol. Its infrared spectrum showed an enol band at 6.28 μ .

Anal. Calcd. for $C_{34}H_{30}CuO_4$: C, 71.95; H, 5.34; Cu, 11.22. Found: C, 71.84; H, 5.71; Cu, 10.90.

A sample of **27** was heated on a steam bath with cyanoacetamide and aqueous sodium carbonate for 2 hr. The mixture was cooled and acidified with acetic acid. The precipitate was collected and recrystallized from ethanol to give 5-phenyl-6-(β -phenylethyl)-3-cyano-2(1)-pyridone (**30**) in 50% yield; its melting point was 285–286° after three recrystallizations from ethanol. The infrared spectrum of the pyridone showed an amide band at 6.03 μ .

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.36; N, 9.32. Found: C, 79.72; H, 5.19; N, 9.21.

A sample of **27** was deformed with hot sodium hydroxide solution to form 1,4-diphenyl-2-butanone (**28**), which was isolated in 87% yield as its semicarbazone, m.p. 127–128° after recrystallization from 75% ethanol (lit.¹⁶ m.p. 129–130°).

Ketone **28** was independently synthesized from di- β -phenylethylcadmium and phenylacetyl chloride. The cadmium reagent was prepared by treating a cooled solution of the Grignard reagent of 0.22 mole of β -

phenylethyl bromide in ether with 0.109 mole of finely powdered, dried cadmium chloride. The suspension was refluxed until there was no Gilman test and the ether replaced by benzene. The suspension was heated to reflux and 15.5 g. (0.1 mole) of phenylacetyl chloride was added as rapidly as possible. The mixture was stirred under reflux for 3 hr., then stirred for 8 hr. at room temperature. The complex was decomposed with 50% sulfuric acid and ice. The benzene layer, combined with two benzene extracts of the aqueous layer, was washed with water, 5% aqueous sodium carbonate, and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated. The residue was distilled under reduced pressure to give 15.5 g. (70%) of ketone **28**, b.p. 157–158° at 7 mm. The semicarbazone, recrystallized from 75% ethanol, melted at 130–131°, undepressed on admixture with a sample of the semicarbazone of ketone **28** obtained on deformylation of **27**.

Ketone **28** (10.0 g., 0.04 mole) was formylated with 3.5 g. (0.047 mole) of ethyl formate by means of sodium ethoxide (prepared from 1 g., 0.044 g.-atom of sodium) in 50 ml. of absolute ethanol (stirred for 12 hr.). The reaction mixture was worked up to give 5 g. (50%) of crude β -ketoaldehyde **27**, which was isolated as its green copper chelate **29**, m.p. 137–138°, undepressed on admixture with a sample of the chelate prepared as described above. The infrared spectra of the two samples were identical.

(16) A. Y. Berlin and Y. V. Markova, *Zh. Obshch. Khim.*, **18**, 1791 (1948).

Trifluoroacetanilide. pK_a and Alkaline Hydrolysis Kinetics

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The rate of hydrolysis of trifluoroacetanilide levels off at high pH. This occurs at a pH well above the pK_a of the anilide and is therefore not due, as previously suggested, to formation of an unreactive anion. In fact, the rate data indicate that an anionic species of the substrate is reactive, giving hydrolysis products in a reaction first order in this species and in hydroxide. This reaction predominates at high pH. Its rate approaches a limiting value as pH is increased, accounting for the observed leveling off in hydrolysis rate. It is proposed that this leveling off is due to a limitation imposed by the rate of formation of the reactive anionic species. The hydrolysis rates and their salt effects are in agreement with this explanation. The hydrolysis is catalyzed by mono-, di-, and triethanolamine and morpholine buffers. The last gives nonlinear dependence of rate on buffer concentration.

Trifluoroacetanilide ($C_8H_8NHCOCF_3$) hydrolyzes in alkaline solutions to give aniline and trifluoroacetate ion. Hydrolysis rates in 0.006–0.557 *M* sodium hy-

droxide were measured by Biechler and Taft.¹ The pseudo-first-order rate constant increases with pH but not linearly. Rather, it approaches a limiting value. This behavior was attributed to dissociation of the nitrogen proton to give an unreactive anion.¹ A pK_a value of 11.9 (25°) for the anilide was calculated from the rate data. This interpretation of the data is apparently incorrect, for it has now been found by spectrophotometry that pK_a for trifluoroacetanilide is 9.5 at 25°. The ultraviolet absorption spectrum of the anilide shows a pronounced change with pH in the vicinity of 9.5. There is no change with pH in the higher pH region within which the hydrolysis rate levels off. This paper presents additional rate data, extending to pH values below the pK_a of the anilide. It also suggests a mechanism to explain the rate data.

Results

The log hydroxide concentration–log rate profile for the hydrolysis of trifluoroacetanilide in water con-

(1) S. S. Biechler and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4927 (1957).

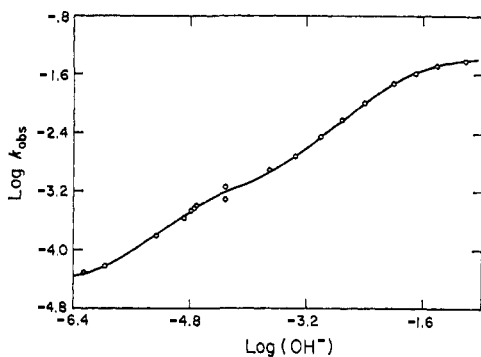


Figure 1. Rate profile for hydrolysis of trifluoroacetanilide at 25° and ionic strength 0.100: points, experimental values; curve, calculated with eq. 3 and parameter values of Table IV.

taining 0.4 vol. % methanol at 25° and ionic strength 0.100 is shown in Figure 1. There is an inflection in the vicinity of the spectrophotometrically determined pK_a . Numerical values for the rate constants for ionic strengths 0.010, 0.040, and 0.100 are collected in Table I. The observed pseudo-first-order rate constant

Table I. Pseudo-First-Order Rate Constants for the Hydrolysis of Trifluoroacetanilide at 25°

$-\text{Log} [\text{OH}^-]$	Ionic strength	$k_{\text{obsd}} \times 10^3, \text{min.}^{-1}$	$k_{\text{obsd}} (\text{calcd.}^a) \times 10^3, \text{min.}^{-1}$
2.00	0.010	15.24	15.26
2.16	0.010	12.08	11.96
2.305	0.010	9.16	9.35
2.405	0.010	7.88	7.89
2.71	0.010	4.63	4.56
1.40	0.040	31.3	30.7
1.70	0.040	23.7	24.0
2.00	0.040	16.76	16.76
2.305	0.040	10.61	10.52
1.00	0.100	38.0	38.3
1.40	0.100	32.8	32.5
1.70	0.100	25.9	26.0
2.00	0.100	18.7	18.6
2.40	0.100	10.2	10.2
2.71	0.100	5.87	5.93
3.01	0.100	3.48	3.46
3.34-3.36	0.100	1.88	1.96
3.70-3.73	0.100	1.23	1.17
4.28-4.34	0.100	0.483	0.599
4.31	0.100	0.718 ^b	0.599
4.65-4.77	0.100	0.396	0.371
4.68-4.77	0.100	0.371	0.364
4.69-4.86	0.100	0.345 ^c	0.341
4.87	0.100	0.268 ^b	0.298
5.26	0.100	0.155 ^b	0.165
5.96	0.100	0.0607 ^b	0.0612
6.26	0.100	0.0491 ^b	0.0458

^a Calculated with eq. 3 and the parameter values of Table IV.

^b Values obtained by extrapolation to zero buffer concentration.

^c The initial substrate concentration in this experiment was $2.1 \times 10^{-4} M$; in the other experiments it was about $5 \times 10^{-5} M$.

is defined by $-d[S]/dt = k_{\text{obsd}}[S]$, where $[S]$ is the total molarity of all forms of the substrate, and t is the time in minutes. The molarity of hydroxide was known directly from the amount of sodium hydroxide used, or it was calculated (for the lower hydroxide concentrations and for buffered solutions) with $\log (\text{OH}^-) =$

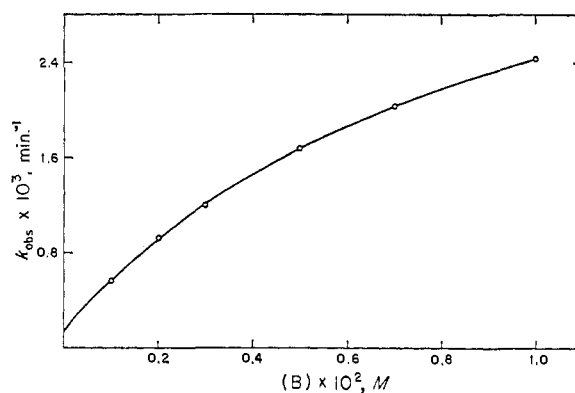


Figure 2. Rates of hydrolysis of trifluoroacetanilide in morpholine buffers having constant buffer ratio, $[\text{BH}^+]/[\text{B}] = 1.0$, but varying total buffer concentration; $[\text{B}] =$ molarity of the basic buffer species; $T = 25^\circ$; ionic strength = 0.100: points, experimental values; curve, calculated with eq. 2.

$\text{pH}_g - 13.83$, where pH_g is the pH measured with glass and calomel electrodes calibrated against 0.01 M borate. This empirical relationship was shown to hold within ± 0.01 log unit for sodium hydroxide concentrations between 4.5×10^{-4} and $10^{-2} M$ (ionic strength adjusted to 0.100 with sodium chloride).

The solutions having the lower hydroxide concentrations were buffered with mono-, di-, and triethanolamine (MEA, DEA, and TEA) and morpholine buffers. These buffers all catalyzed the hydrolysis. The k_{obsd} values given in Figure 1 and Table I for these lower hydroxide concentrations were obtained by measuring the rates for several concentrations of a given buffer (constant pH and ionic strength) and extrapolating to zero buffer concentration. For the MEA, DEA, and TEA buffers, these extrapolations were linear.

$$k_{\text{obsd}} = a_1 + a_2[\text{B}] \quad (1)$$

where $[\text{B}]$ is the molarity of the basic buffer species. The values of a_1 and a_2 for these buffers are given in Table II. The value of a_2 for the TEA buffers was

Table II. Parameters for Equation 1

Buffer	Buffer ratio, $[\text{BH}^+]/[\text{B}]$	$-\text{Log} [\text{OH}^-]$	$a_1 \times 10^4, \text{min.}^{-1}$	$a_2, M^{-1} \text{min.}^{-1}$
TEA	2.0	6.26	0.4911	0.04532
TEA	1.0	5.96	0.6070	0.04479
DEA	1.0	4.87	2.678	0.1655
MEA	1.0	4.31	7.179	0.2923

almost independent of the buffer ratio $[\text{BH}^+]/[\text{B}]$, indicative of general base catalysis. The rate of hydrolysis in the morpholine buffers was not linear in buffer concentration (Figure 2). The data are described closely by the following relation (eq. 2). The

$$k_{\text{obsd}} = 1.550 \times 10^{-4} + [\text{B}]/(2.187 + 221.3 [\text{B}]) \text{min.}^{-1} \quad (2)$$

experimental rate constants for the buffered solutions and the values calculated with eq. 1 and 2 are given in Table III.

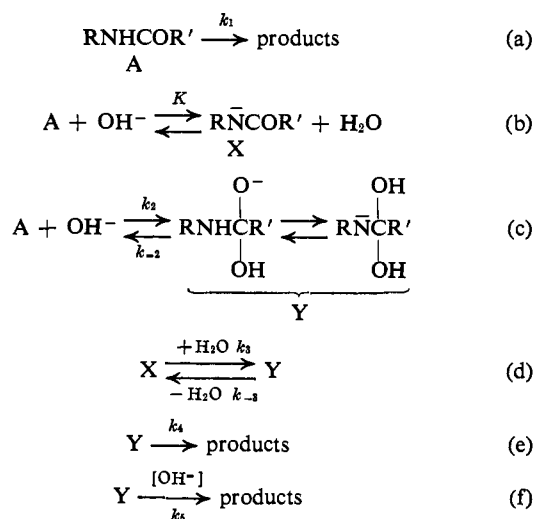
Table III. Hydrolysis Rates in Buffered Solutions at 25° and Ionic Strength 0.100

Buffer	[B] × 10 ² , M	k _{obsd} × 10 ³ , min. ⁻¹	k _{obsd} (calcd. ^a) × 10 ³ , min. ⁻¹
TEA ^b	0.5	0.0718	0.0718
TEA ^b	1.0	0.0916	0.0944
TEA ^b	1.5	0.121	0.117
TEA ^b	2.5	0.165	0.162
TEA ^b	3.5	0.203	0.208
TEA ^b	5.0	0.278	0.276
TEA	1.0	0.106	0.105
TEA	2.0	0.150	0.150
TEA	3.0	0.197	0.195
TEA	5.0	0.285	0.285
TEA	7.0	0.371	0.374
TEA	10.0	0.510	0.509
DEA	1.0	0.419	0.433
DEA	2.0	0.612	0.599
DEA	3.0	0.774	0.764
DEA	5.0	1.109	1.095
DEA	7.0	1.39	1.43
DEA	10.0	1.94	1.92
MEA	1.0	0.986	1.010
MEA	2.0	1.30	1.30
MEA	3.0	1.59	1.59
MEA	5.0	2.23	2.18
MEA	7.0	2.79	2.76
MEA	10.0	3.60	3.64
Morpholine ^c	1.0	0.566	0.570
Morpholine	2.0	0.926	0.915
Morpholine	3.0	1.200	1.207
Morpholine	5.0	1.68	1.67
Morpholine	7.0	2.03	2.03
Morpholine	10.0	2.43	2.43

^a Calculated with eq. 1 and the parameter values of Table II in the case of the TEA, DEA, and MEA buffers and with eq. 2 in the case of the morpholine buffers. ^b Buffer ratio [BH⁺]/[B] = 2.0; in all other cases it was 1.0. ^c -Log [OH⁻] for the morpholine buffers was 5.26.

Discussion

The rate data of Table I are interpreted on the basis of the following mechanism



where R = phenyl and R' = CF₃. The reaction path for the general base catalyzed hydrolysis in which the substrate acts as the catalyst has been left out of the mechanism. In the experiments, the concentration of the substrate was sufficiently low that the contribution by this catalyzed reaction was unimportant. The

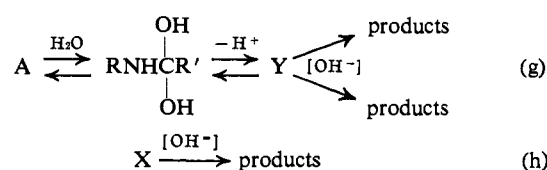
constants k_2 and k_5 are second-order rate constants; the other k values are first order. The equilibrium constant K is defined by $K = [X]/([A][\text{OH}^-])$. The concentration of Y is assumed to be negligible in comparison with [A] + [X]. Therefore, K is very nearly equivalent to the spectrophotometrically determined equilibrium constant for the reversible reaction of A with hydroxide. The proton transfer reactions are considered to be sufficiently fast that the species involved maintain their equilibrium concentrations with respect to these reactions. The leveling off in hydrolysis rate at high pH is due to the failure of Y to maintain its equilibrium concentration with respect to the carbonyl addition reactions (c and d). As pH is increased, the formation of Y in these reactions tends to become rate determining.

Use of the steady-state approximation for [Y] leads to the following expression for the observed pseudo-first-order rate constant.

$$k_{\text{obsd}} = \frac{1}{1 + K[\text{OH}^-]} \left\{ k_1 + \frac{(k_2 + k_3K)(k_4 + k_5[\text{OH}^-])[\text{OH}^-]}{k_{-2} + k_{-3} + k_4 + k_5[\text{OH}^-]} \right\} \quad (3)$$

Parameter values giving a fit of eq. 3 to the experimental k_{obsd} values are presented in Table IV. These parameter values were determined with an IBM 1620 computer programmed for nonlinear regression. In this determination, the k_{obsd} values were weighted approximately in inverse proportion to their standard errors. In those cases in which there was a measurable decrease in hydroxide concentration during the reaction (see Table I), the values of [OH⁻] corresponding to the mean values of -log [OH⁻] were used in the parameter evaluation. For the experiments at ionic strengths 0.010 and 0.040, the hydroxide concentration did not extend low enough to allow determination of all five parameters of eq. 3. However, k_5 , being the rate constant for the reaction of two charged species, is the only one of the constants in eq. 3 which would be expected, on theoretical grounds, to vary appreciably with ionic strength.² It was assumed, therefore, that the parameters K , k_1 , and $k_4/(k_{-2} + k_{-3})$ have the same values at all three ionic strengths. The values of these parameters for ionic strength 0.100 were substituted in eq. 3, and then the remaining two parameters, $k_2 + k_3K$ and $k_5/(k_{-2} + k_{-3})$, were evaluated by nonlinear regression fitting of the equation to the experimental k_{obsd} values for ionic strengths 0.010 and 0.040. Calculated k_{obsd} values, obtained with eq. 3 and the parameter values of Table IV, are given in Figure 1 and Table I.

Although reactions a-f are sufficient to account for the rate data, the following additional paths cannot be completely excluded. As the hydroxide concentration is decreased, the steady-state concentration of Y



(2) C. W. Davies, "Progress in Reaction Kinetics," Vol. 1, Pergamon Press Inc., New York, N. Y., 1961, p. 161.

Table IV. Parameter Values for Equation 3

Parameter	Ionic strength		
	0.010	0.040	0.100
$K \times 10^{-4}, M^{-1}$	4.31 ^a	4.31 ^a	4.31 ± 0.03
$k_1 \times 10^5, \text{min.}^{-1}$	3.04 ^a	3.04 ^a	3.04 ± 3.44
$(k_2 + k_3K) \times 10^{-3}, M^{-1} \text{min.}^{-1}$	1.918 ± 0.163 ^b	1.853 ± 0.052	1.877 ± 0.550
$k_4(k_{-2} + k_{-3}) \times 10^2$	1.676 ^a	1.676 ^a	1.676 ± 0.205
$k_5/(k_{-2} + k_{-3}), M^{-1}$	50.7 ± 6.1	62.5 ± 3.3	73.4 ± 1.6

^a Not calculated from the rate data for this ionic strength, but assumed to be equal to the value for ionic strength 0.100. ^b The limits given are the estimates of the standard errors.

approaches its unperturbed equilibrium value, and path g becomes less and less kinetically distinguishable from the other paths through Y. Thus, whereas it can be concluded from the rate data that path g is of relatively little importance in the upper part of the experimental pH range, no such conclusion can be reached in regard to the lower part of the range. Now, consider path h. Reaction along this path has the effect of diminishing the leveling off in rate at high pH. If all reaction occurred *via* h, the rate would continue to increase linearly with [OH⁻]. The degree to which the rate levels off at high pH indicates that path h is not of much importance in the experimental pH range. In view of possible experimental errors in the rate constants, however, reaction *via* h cannot be ruled out completely. It could contribute several per cent to the total reaction at the upper end of the pH range.

The value of k_1 , the rate constant for the solvent-catalyzed reaction, is poorly defined by the rate data, as indicated by its large standard error (Table IV). Approximate rate measurements for weakly acidic, unbuffered solutions indicate that k_1 is probably smaller than $1 \times 10^{-5} \text{ min.}^{-1}$. The value of K from the rate data is $4.31 \times 10^4 M^{-1}$. The value determined independently by spectrophotometry is $2.0 \times 10^4 M^{-1}$. This discrepancy does not appear to be entirely explicable on the basis of normally distributed errors or reasonable systematic errors. Therefore, it may indicate a weakness in the theoretical treatment. There is little doubt, however, that the inflection in the rate profile of Figure 1 is associated with the acid-base reaction of the substrate.

As expected,² the parameter $k_2 + k_3K$ shows little salt effect. The change in $k_5/(k_{-2} + k_{-3})$ with ionic strength may be assumed to be due primarily to change in k_5 .² A plot of $\log [k_5/(k_{-2} + k_{-3})]$ vs. $[\mu^{1/2}/(1 + \mu^{1/2}) - 0.20\mu]$, where μ is the ionic strength, falls near to a straight line of unit positive slope. This is the expected result, k_5 being the rate constant for the reaction of two singly charged anions.²

As [OH⁻] in eq. 3 approaches infinity, eq. 3 approaches the limiting form

$$k_{\text{obsd}}^{\text{lim}} = (k_2 + k_3K)/K \quad (4)$$

Equation 4, with parameter values of Table IV, gives $k_{\text{obsd}}^{\text{lim}} \cong 0.044 \text{ min.}^{-1}$. This value agrees well with the limiting value of k_{obsd} ($\sim 0.0455 \text{ min.}^{-1}$ at 25.5°) obtained by Biechler and Taft.¹

There is evidence that tetrahedral carbonyl addition compounds, such as are proposed in the mechanism, may be intermediates in the alkaline hydrolysis of

amides.³ It is interesting to note that reaction f is of the type invoked by Biechler and Taft to explain hydrolysis rate data for N-methyltrifluoroacetanilide.¹ According to their interpretation of data for trifluoroacetanilide, however, there appeared to be no reaction of this type involved in the hydrolysis of trifluoroacetanilide. This seeming inconsistency in the behavior of the two anilides defied explanation; apparently it does not really exist, being due to erroneous interpretation of their data for trifluoroacetanilide. The ratio, k_5/k_4 , of the rate constants for reactions f and e is ~ 4000 for trifluoroacetanilide, whereas it is ~ 200 for N-methyltrifluoroacetanilide.¹

Experimental

Trifluoroacetanilide,⁴ m.p. $87.5\text{--}88.5^\circ$ uncor., was prepared⁵ by the reaction of aniline and trifluoroacetic anhydride in acetonitrile. It was recrystallized from aqueous ethanol. Mono-, di-, and triethanolamines were Eastman Grade. The morpholine was Eastman Practical Grade. Gas chromatography of the morpholine indicated the presence of only one volatile substance. Sodium chloride was General Chemical Reagent Grade. "Acculute" sodium hydroxide and hydrochloric acid solutions were used in the unbuffered and amine-buffered systems, respectively. The laboratory-distilled water which was used in the experiments gave pH readings rising to and leveling off at about 7.9 when the water was purged with nitrogen for about 45 min., indicating the presence of traces of basic impurity.⁶

Hydrolysis reactions, conducted in polyethylene vessels at $25 \pm 0.2^\circ$, were started by adding small volumes of nitrogen-purged sodium hydroxide solution or buffer solution to nitrogen-purged solutions of the substrate and sufficient sodium chloride to give the desired ionic strength. The incorporation of the trifluoroacetanilide was facilitated by dissolving it first in a small amount of methanol and then diluting this solution with water to give a stock solution. In all reaction mixtures, the concentration of methanol was 0.4 vol. %. A slow stream of nitrogen was passed continuously during the reactions. Flow rate was increased during and for several minutes after removal of samples. For reactions lasting more than 8 hr., the nitrogen was first passed through 0.1 M sodium hydroxide and 0.1 M sodium chloride. For reactions in weakly alkaline, unbuffered solutions, pH was

(3) M. L. Bender and R. D. Ginger, *J. Am. Chem. Soc.*, **77**, 348 (1955); E. Whalley, *Advan. Phys. Org. Chem.*, **2**, 138 (1964).

(4) F. Swarts, *Bull. Sci. Acad. Roy. Belg.*, **8**, 343 (1922); *Chem. Abstr.*, **17**, 769 (1923).

(5) Prepared by Mr. R. G. Cameron, of the Eastman Kodak Co.

(6) S. B. Ellis and J. J. Kiehl, *J. Am. Chem. Soc.*, **57**, 2145 (1935).

monitored with a Leeds and Northrup Black Dot glass electrode, a Beckman calomel electrode, and a Beckman Model GS meter. Samples of reaction mixture were removed from time to time and the absorbance was measured with the Beckman DU spectrophotometer. The wave length (262.4 m μ) of the isobestic point for the acid-base reaction of the substrate was used. Readings at this wave length gave a direct indication of the concentration of substrate and products without the necessity of knowing the fractions of the substrate in the acid and base forms. First-order rate constants were obtained from the slopes of the linear log ($A_t - A_\infty$) vs. t plots, where the absorbance at infinite time, A_∞ , was that of aniline and of the other ingredients (sodium hydroxide, sodium chloride, buffer) or of absorbing impurities associated with these ingredients. Trifluoroacetate ion has negligible absorbance at 262.4 m μ . The slopes were obtained by linear regression with an IBM 1620 computer. To make an approximate allowance for differences in the probable errors in the values of log ($A_t - A_\infty$), these values were weighted in proportion to $A_t - A_\infty$.

The acid-base equilibrium constant for trifluoroacetanilide is given by $K = [C]/([A][OH^-])$, where $[C]$ is the concentration of amide species bearing a single negative charge and $[A]$ is the concentration of the uncharged species. Hydroxide concentration was calculated with the empirical relation, $-\log [OH^-] = 13.83 - \text{pH}_g$, where pH_g is the pH measured with the glass and calomel electrodes calibrated against 0.01 M borate. Values of $[C]/[A]$ were determined in the usual way from absorbance measurements (245 m μ) extrapolated back to the time of mixing the nitrogen-purged amide and sodium hydroxide solutions. For five experiments at 25° and ionic strength 0.100 (sodium chloride), in which the value of $[C]/[A]$ ranged from 0.45 to 9.0, a mean value of 4.293 was obtained for log K . The range was 0.019 log unit. This value for log K corresponds to a $\text{p}K_a$ of 9.54, where $\text{p}K_a$ is defined by $\text{p}K_a = \text{pH}_g - \log ([C]/[A]) = 13.83 - \log K$.

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The Kinetics of the Hydrolysis of 6-Trichloromethylpurine in Dilute Aqueous Solutions¹

Sasson Cohen and Nathan Dinar

Contribution from the Israel Institute for Biological Research, Ness-Ziona, Israel.

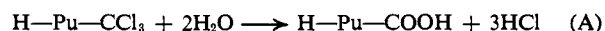
Received March 9, 1965

Above pH 5, the hydrolysis of 6-trichloromethylpurine (HPuCCl₃) to purinoic and hydrochloric acids in dilute, aqueous solutions proceeds as follows. (1) HPuCCl₃ is ionized to (PuCCl₃)⁻, the relative concentration of which depends on the pH and the $\text{p}K_a$ of HPuCCl₃. (2) (PuCCl₃)⁻ loses Cl⁻ in a rate-determining step, yielding a reactive intermediate, Pu=CCl₂. (3) The latter is sufficiently stable to discriminate between various nucleophiles, its relative reaction rates with water, Cl⁻, or OH⁻ being 1, 233, and 1290, respectively. Non-ionized HPuCCl₃ is capable of undergoing hydrolysis, but at a rate much slower than (PuCCl₃)⁻, the first-order rate constants being 8×10^{-7} and 1.09×10^{-3} sec.⁻¹, respectively. The relative stability of the CCl₃ group in HPuCCl₃, compared to structurally related systems, is ascribed to the double bond-no bond resonance of the molecule.

Recently it has been shown that 6-trichloromethylpurine (1) is capable of acylating various substrates with remarkable ease. The reaction with water or alcohols leads to purinoic acid or its esters,² that with amines to N-purinoylamines,^{2,3} and that with phenols

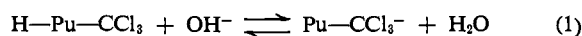
to *o*- or *p*-purinoylphenols.⁴ The course of these reactions was rationalized by assuming the formation, from 1, of a common, highly reactive intermediate by loss of one molecule of hydrogen chloride, similar to the formation of dichlorocarbene from chloroform.⁵ These observations recall also the unusual reactivity of the trifluoromethyl group in certain trifluoromethyl indolecarboxylates⁶ and in 5-trifluoromethyluracil.⁷ In none of these cases, however, has the mechanisms involved been sufficiently elucidated, and it seemed of interest to investigate the kinetics of the acylation reaction with 6-trichloromethylpurine. The acylation of water will be considered first because of the relative simplicity of the treatment involved.

The hydrolysis of 6-trichloromethylpurine leads to purinoic and hydrochloric acids (eq. A) (H—Pu re-



resents purin-6-yl, H being an imidazole hydrogen).

As a working hypothesis, we assume that reaction A proceeds stepwise in the following order.



(4) S. Cohen, E. Thom, and A. Bendich, *J. Org. Chem.*, **28**, 1379 (1963).

(5) J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950); J. Hine, R. C. Peek, Jr., and B. D. Oakes, *ibid.*, **76**, 827 (1954); J. Hine and A. M. Dowell, *ibid.*, **76**, 2688 (1954).

(6) J. Bornstein, S. A. Leone, W. F. Sullivan, and O. F. Bennett, *ibid.*, **79**, 1745 (1957).

(7) C. Heidelberger, D. Parsons, and D. C. Remy, *J. Med. Chem.*, **7**, 1 (1964).

(1) This investigation was supported by Grants CA 06696-01 and -02, from the National Cancer Institute, Public Health Service.

(2) S. Cohen, E. Thom, and A. Bendich, *J. Org. Chem.*, **27**, 3545 (1962).

(3) S. Cohen, E. Thom, and A. Bendich, *Biochemistry*, **2**, 176 (1963).