There were three components and in order of collection off the column these were shown to be 4,7,7-trimethyl-2-azabicyclo[2.2.1]-heptane (**6**), *N*-hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**9**), and 2-*exo*-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (**30**). The reaction was repeated and analysis by vpc on a 10-ft 20% Apiezon L-KOH on 60–80 Chromosorb P analytical column (*vs. N,N*-dimethylaniline as internal standard) gave 13.4% of **6**, 60.4% of 9, and 15.3% of **30**.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for a grant which supported this investigation.

Diffusion-Controlled Proton Transfer and Heavy-Atom Reorganization in the General Acid, Specific Base Catalyzed Hydrolysis of Amides[1]

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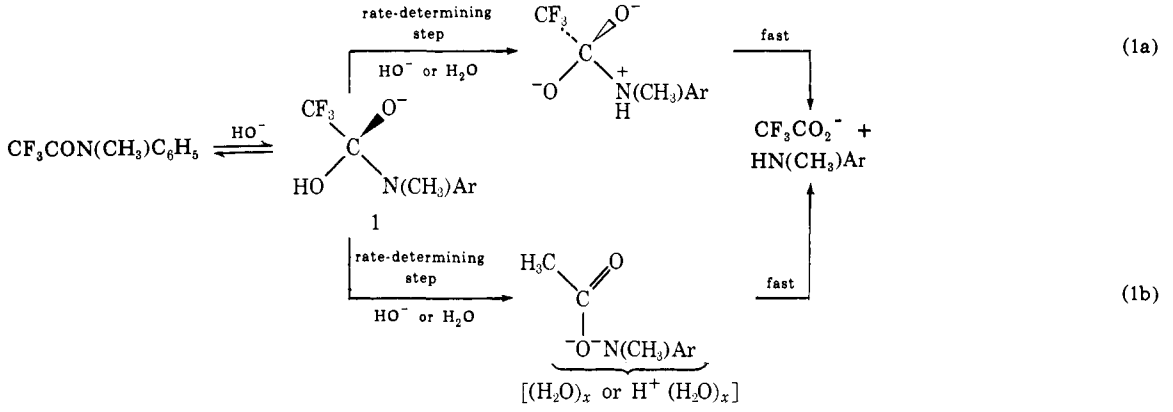
Abstract: The acyl-activated amide $CF_3CON(CH_3)C_6H_5$ adds hydroxide ion without general catalysis to form a tetrahedral intermediate which decomposes to *N*-methylaniline and trifluoroacetate ion with general acid and general base catalysis. General acids have $\delta_{BH} \log k_{BH} \simeq \delta_{BH} \log K_{BH}$ and thus are completely dissociated in the transition state. The glycine-catalyzed reaction is accelerated twofold by either a *p*-CH_3 or a *m*-Br substituent in the anilide ring, indicating two parallel pathways for catalysis, one with average negative charge and one with average positive charge on the transition state nitrogen, relative to its reactant charge. The former is presumably a diffusion process, the latter spectator catalysis.

In the action of acyl-transfer enzymes, protons are often transferred to and from intermediate tetrahedral carbonyl adducts in the course of their formation or decomposition.[4] The role of these proton shifts in the catalytic process is unknown, although in one proposal, the presumed capacity of the enzyme for precise orientation of the proton donor and acceptor along a highly preferred line for proton transfer is viewed as the origin of a major part of the catalytic power of the enzyme.[5] In the closely related nonenzymatic hydrolysis of amides (eq 1), we found simple proton transfer to the leaving group in the tetrahedral intermediates to be rate determining for poor leaving groups ($pK_b < 9$, eq 1a) with C–N bond cleavage subsequent and fast, while good leaving groups ($pK_b > 9$, eq 1b) suffered rate-limiting fission of the C–N bond, followed by fast proton transfer.[6] This result, although it is in close agreement with other studies of different amides[7] and with substituent-effect and isotope-effect data on α-chymotrypsin,[8] refers only to catalysis by water and hydroxide ion. Because of the undoubted part played by general acid–base catalysis in enzyme action, we have examined the same system in the presence of ten buffers of $pK_a = 8.3$–10.6. The kinetic complexity of



(1) Amide Hydrolysis. VI. For part V, see R. L. Schowen, C. R. Hopper, and C. M. Bazikian, *J. Amer. Chem. Soc.*, **94**, 3095 (1972). This research was supported by the National Science Foundation and the National Institutes of Health and was carried out in part at the Computation Center of the University of Kansas. Further details may be found in D. Drake, Ph.D. Thesis, University of Kansas, 1971.

(2) Gulf Oil Corporation Fellow, 1969–1970.

(3) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

(4) (a) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 218–226; (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapters 1 and 2.

(5) J. H. Wang, *Proc. Nat. Acad. Sci. U. S.*, **66**, 874 (1970).

(6) (a) L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 2014 (1971). The result was predicted in (b) R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *ibid.*, **88**, 4008 (1966).

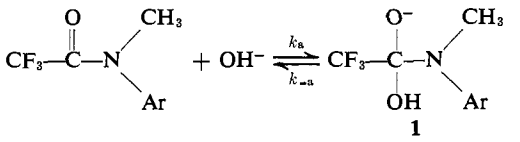
(7) (a) J. M. Moreau, M. Annez de Taboada, P. van Brandt, and A. Bruylants, *Tetrahedron Lett.*, 1255 (1970); (b) R. M. Pollack and M. L. Bender, *J. Amer. Chem. Soc.*, **92**, 7190 (1970); (c) S. S. Biechler and R. W. Taft, Jr., *ibid.*, **79**, 4927 (1957).

(8) (a) T. Inagami, S. S. York, and A. Patchornik, *ibid.*, **87**, 126 (1965); (b) L. Parker and J. H. Wang, *J. Biol. Chem.*, **243**, 3729 (1968).

these systems limits the precision of our catalytic constants and prevents the use of solvent isotope effects, a powerful tool in the previous work. We employ only free-energy relationships, but the result is clear: the scheme of eq 1 is inadequate for general catalysis.

Results

Kinetics. In agreement with previous studies[9,10] on the hydrolysis of acyl-activated acetanilides in buffers, *N*-methyl-2,2,2-trifluoroacetanilide was found to undergo superimposed general catalysis of hydroxide-induced hydrolysis in buffers the pK_a's of which ranged from 8.3 to 10.6. General catalysis was also found with *m*-bromo- and *p*-methyl-*N*-methyltrifluoroacetanilide in glycine buffers. The observed first-order rate constants k_0 are, at low buffer concentrations, linear in buffer concentration at constant pH, but at high buffer concentrations, the values of k_0 climb to a plateau independent (within experimental error) of buffer concentration.[11] This behavior is consistent with a two-step process like that observed in nonbuffer, hydroxide catalysis, in which the second step is subject to general catalysis. The mechanism for general catalyzed hydrolysis is given in eq 2. By application of the steady-



(2a)

$$\mathbf{1} \xrightarrow[k_B'[B] + k_{BH}'[BH]]{k_1' + k_2'[HO^-] +} CF_3CO_2^- + C_6H_5NHCH_3 \qquad (2b)$$

state assumption for **1**, an expression for k_0 may be obtained, in terms of k_a and k_{-a}, the rate constants for formation and reversion back to reactants, respectively, of **1** and k_1', k_2', k_B', and k_{BH}', rate constants for decomposition of **1** to products (eq 3). Multiplication of

$$k_0 = \frac{k_a[HO^-](k_1' + k_2'[HO^-] + k_B'[B] + k_{BH}'[BH])}{k_{-a} + k_1' + k_2'[HO^-] + k_B'[B] + k_{BH}'[BH]} \qquad (3)$$

the numerator and denominator of eq 3 by k_a/k_{-a} generates new rate constants k_1, k_2, k_B, and k_{BH}, in which k_1 ($\equiv k_ak_1'/k_{-a}$) and k_2 ($\equiv k_ak_2'/k_{-a}$) are rate constants for converting reactants to the water and hydroxide-catalyzed transition states, respectively, for breakdown of the tetrahedral adduct **1** to products; k_B ($\equiv k_ak_B'/k_{-a}$) and k_{BH} ($\equiv k_ak_{BH}'/k_{-a}$) pertain to transformation of the reactants to the general base and general acid catalysis transition states, respectively, for decomposition of **1** to products. This leads to eq 4, in which all rate con-

$$k_0 = \frac{k_a[HO^-](k_1 + k_2[HO^-] + k_B[B] + k_{BH}[BH])}{k_a + k_1 + k_2[HO^-] + k_B[B] + k_{BH}[BH]} \qquad (4)$$

stants relate a transition state to the original reactant state.

According to eq 4, at high buffer strength (where $k_{BH}[BH] + k_B[B] \gg k_a + k_1 + k_2[HO^-]$) the asymptotic value of k_0, barring other kinetically important reactions, should be equal to $k_a[HO^-]$. The limiting values of k_0 were in fact equal to the associated values of $k_a[HO^-]$. More than 400 k_0 values were compiled in the study presented here but are not given in order to save space. A listing is available on request from us.

Data Treatment. Evaluation of k_B and k_{BH} was accomplished in most cases by adjusting the experimental k_0's to fit eq 4 by a nonlinear least-squares program.[12] The values of k_a, k_1, and k_2 were available from earlier work.[6] The three input variables k_0, [OH$^-$], and [B] may be varied independently in the program allowing for its application to cases where the [B]/[BH] ratio was not held constant. The final computation step in the program involves the solution of the (simultaneous) normal equations of curve fitting. These equations may form an ill-conditioned set,[6a,13] so that small variations in the coefficients (which are subject to experimental errors) may cause enormous variation in the solutions. A value greater than ten for any element of the inverse of the normalized coefficient matrix is diagnostic for this situation.[14] The fitting of the rate data for benzylamine buffers with the unsubstituted anilide and for the *m*-bromo- and *p*-methylanilides in glycine buffers gave rise to ill-conditioned normal equations according to this test. The least-squares value of k_{BH} for benzylamine is acceptable, however, because ill-conditioning did not set in until the value of the solution to the normal equations (the difference between the trial value and the newly calculated value of the rate constant) was so small compared with the calculated value of the rate constant that the resulting large uncertainty in the solution is tolerable. For the other ill-conditioned data, an alternate procedure was used to evaluate k_{BH} and k_B as follows. Equation 4 may be rearranged to give eq 5. A plot of $k_0k_a/(k_a[HO^-] - k_0)$

$$(k_0k_a)/(k_a[HO^-] - k_0) = (k_{BH}[BH]/[B] + k_B)[B] + k_1 + k_2[HO^-] \qquad (5)$$

vs. [B] for a constant [BH]/[B] ratio is linear with a slope equal to $k_{BH}([BH]/[B]) + k_B$. Plotting the slope of the line for each buffer ratio as a function of [BH]/[B] gives a straight line whose slope is k_{BH} and whose intercept is k_B. Calculated values of k_B and k_{BH} along with error limits are presented in Table I. Cross-checking of calculations by graphical and computer techniques showed no differences when ill-conditioning was absent.

Discussion

The rate constants in Table I refer to conversion of original reactants (anilide A, hydroxide ion, and general catalyst) to the transition state for general acid (k_{BH}) or general base (k_B) catalyzed decomposition of the tetrahedral intermediate (**1** in eq 1 and 2) to products. The values of k_B are so imprecise that we will not further consider them here. In the general acid catalyzed process, the degree of proton transfer from the general acid to the rest, T, of the transition state (eq 6), corre-

(9) Very extensive and valuable work of S. O. Eriksson and his collaborators is reviewed in (a) S. O. Eriksson, *Acta Pharm. Suecica*, **6**, 139 (1969); see especially (b) S. O. Eriksson, *Acta Chem. Scand.*, **22**, 892 (1968).

(10) (a) P. M. Mader, *J. Amer. Chem. Soc.*, **87**, 3191 (1965); (b) R. L. Schowen and G. W. Zuorick, *ibid.*, **88**, 1223 (1966); (c) R. Pratt and J. M. Lawlor, *J. Chem. Soc. B*, 230 (1969).

(11) The same sort of behavior has been observed by Mader[10a] and by Eriksson.[9]

(12) The program was described by Kershner and Schowen[6a] and was not modified substantially in its use here.

(13) The same phenomenon has recently arisen in certain statistical analyses of biological data by D. R. Hudson, G. E. Bass and W. P. Purcell, *J. Med. Chem.*, **13**, 1184 (1970).

(14) A. Ralston, "A First Course in Numerical Analysis," McGraw-Hill, New York, N. Y., 1965, p 397.

Table I. Rate Constants for General Acid and Base Catalysis in the Alkaline Hydrolysis of $CF_3CON(CH_3)C_6H_4X$ in Water at 25.0 ± 0.1° (μ = 0.05)[a]

Catalyst system (BH)[b]	X	k_{BH}, M^{-2} sec^{-1}	k_B, M^{-2} sec^{-1}
(1) *N*-Glycylglycine	H	2602 ± 295	177 ± 125
(2) Ammonium	H	4109 ± 1200	100 ± 150[c]
(3) Benzylammonium	H	4203 ± 937	33 ± 275[c]
(4) Glycine	H	1371 ± 195	285 ± 118
	p-CH_3	2620 ± 640	−231 ± 380[c]
	m-Br	2998 ± 440	−180 ± 200[c]
(5) Trimethylammonium	H	1379 ± 456	312 ± 273
(6) *N,N*-Dimethylglycine	H	353 ± 147	192 ± 112
(7) Sarcosine	H	973 ± 162	56 ± 92[c]
(8) β-Alanine	H	808 ± 181	297 ± 142
(9) L-Proline	H	460 ± 121	475 ± 125
(10) *n*-Butylammonium	H	458 ± 120	593 ± 185

[a] Ionic strength maintained with added KCl. [b] Numbers refer to Figure 1. [c] These values, whether positive or negative, are within experimental error of zero and indicate that the contribution of base catalysis in these cases is smaller than the (large) experimental error.

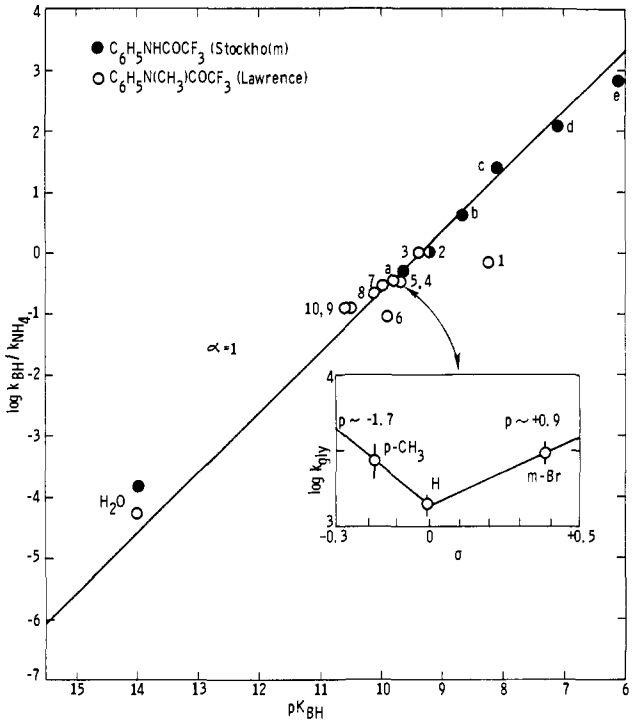


Figure 1. Brønsted plot, normalized to ammonium ion, for general acid catalysis of the hydroxide-induced hydrolysis of 2,2,2-trifluoroacetanilide and *N*-methyl-2,2,2-trifluoroacetanilide. Numbers refer to the catalysts in Table I; pK_{BH} values are from Table II. The open circles represent our data, obtained in Lawrence for the *N*-methyl compound. The filled circles portray points from Eriksson's laboratory in Stockholm.[9b] The letters refer to the following catalysts: (a) β-hydroxyethylammonium ion, (b) morpholinium ion, (c) hydrazinium ion, (d) imidazolium ion, (e) hydroxylammonium ion. The solid line has unit slope.

$$A + HO^- + BH \xrightarrow{k_{BH}} \underset{\alpha \quad 1-\alpha}{[T\text{------}H\text{------}B]} \qquad (6)$$
$$\mathbf{2}$$

sponding to the bond order α in structure **2**, can be measured by comparing the effect of B structure on the free energy of activation ΔG^*_{BH} (proportional to $-\log k_{BH}$) with the effect of B structure on the free energy of ionization of BH, $\Delta G°_{BH}$ (proportional to pK_{BH}), using the Brønsted equation (eq 7).[15] The Brønsted α of eq 7 should be roughly equal to the α of structure **2**. If $\alpha = 0$ in **2**, the BH unit of the reactants is still intact in **2** and effects of B structure on the free energies of **2** and BH should cancel, making $\delta_B \log k_{BH} = 0$ for all BH. At the other extreme, if $\alpha = 1$ in **2**, the BH unit of **2** is completely dissociated and the free energy of **2** should vary with structure exactly as does the free energy of B; thus $-\delta_B \log k_{BH} = \delta_B pK_{BH}$. Between these extremes, in the absence of complicating factors, α should provide a numerical measure of the extent to which B in the transition state has come to resemble B as an independent molecule, *i.e.*, the degree of proton transfer in **2**.

$$-\delta_B \log k_{BH} = \alpha \delta_B pK_{BH} \qquad (7)$$

The Brønsted plot of our data and those of Eriksson[9b] appears in Figure 1. Because Eriksson employed a different substrate ($CF_3CONHC_6H_5$), we plot the data normalized to the common catalyst ammonium ion (thus $\log k_{BH}/k_{NH_4}$ *vs.* pK_{BH}). All the data are satisfactorily fitted by the line of unit slope shown in Figure 1, even the points for "water catalysis" showing only a small positive deviation. Therefore, the catalytic acid appears to be completely ionized in the transition state, a result which would be surprising if the proton-transfer process itself were a component of the reaction coordinate in the transition state. A simple mechanistic model, based on the work of Eigen and his collaborators,[16] which explains the unit Brønsted slope is given in Scheme I. Here the tetrahedral intermediate **1**, formed in a rapid, reversible reaction (eq 8), diffuses together with the catalyst (eq 9); a proton is transferred (presumably to the nitrogen of **1**) in a reaction (eq 10)

(15) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1962, pp 156 ff. It has been shown by F. G. Bordwell, W. J. Boyle, Jr., J. A. Hautala, and K. C. Yee, *J. Amer. Chem. Soc.*, 91, 7224 (1969), that the theoretical limits of 0 and 1 for α may be transgressed in cases where A. J. Kresge (*ibid.*, **92**, 3210 (1970)) has suggested intramolecular electrostatic effects are important. A. J. Kresge, H. L. Chen, Y. Chiang, E. Murill, M. A. Payne, and D. S. Sagatys (*ibid.*, **93**, 413 (1971)) have shown that α may be in error by at least 0.1 as a measure of fractional proton transfer in transition states for protonation of vinyl ethers by carboxylic acids. F. G. Bordwell and W. J. Boyle, Jr., *ibid.*, **93**, 511, 512 (1971), have argued that neither Brønsted slopes nor isotope effects are good quantitative indications of transition-state structure in proton transfers to and from carbon. Nevertheless, for the rough use intended in this paper, the traditional interpretation of α is more than sufficient. Solvation effects (E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, pp 17–20) should not much affect free-energy correlation slopes because of mutual cancellation of the associated enthalpy and entropy changes near room temperature (J. W. Larson and L. G. Hepler in "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969; R. L. Schowen, *J. Pharm. Sci.*, **56**, 931 (1967)).

(16) M. Eigen in "Fast Reactions and Primary Processes in Chemical Kinetics: Nobel Symposium 5," S. Claesson, Ed., Almqvist and Wiksell, Stockholm, 1967; M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964); see also ref 4a, pp 207–217.

Scheme I

$$A + HO^- + BH \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} 1 + BH \quad (8)$$

$$1 + BH \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} \{1, BH\} \quad (9)$$

$$\{1, BH\} \underset{k_b}{\overset{k_t}{\rightleftharpoons}} \{1H, B\} \quad (10)$$

$$K = k_t/k_b = K_{BH}/K_{1H}$$

$$\{1H, B\} \xrightarrow{k_r} CF_3CO_2^- + CH_3NHAr + BH \quad (11)$$

$$\{1H, B\} \xrightarrow{k_{-d}} 1H + B \quad (12)$$

$$1H + B \xrightarrow{\text{fast}} CF_3CO_2^- + CH_3NHAr + BH \quad (13)$$

with an equilibrium constant K fixed by the relative acidities of catalyst (K_{BH}) and N-protonated tetrahedral intermediate (K_{1H}). Now a competition arises between direct decomposition of **1H** in the solvent cage (eq 11) and its diffusion apart from B and subsequent decomposition (eq 12 and 13). Direct decomposition in the solvent cage (eq 11), if it occurs, does not involve assistance by B since $\alpha = 1$. B is thus a *spectator catalyst* in such a process.[6a] Noting that the reaction of eq 8 is always rapid and applying the steady-state assumption to all intermediates in Scheme I, we obtain eq 14a for k_{BH}. Since $k_f/k_b = K_{BH}/K_{1H}$, eq 14b results. Finally we recall that in Eigen's proton-transfer mechanism, the proton switch (k_f or k_b) is always much faster in the exergonic direction than is diffusion out of the solvent cage (k_{-d}). Thus if $K_{BH} < K_{1H}$ so that the k_b reaction in eq 10 is exergonic, then $k_b \gg k_{-d}$ and $k_b \gg k_f$ so that the first term in the denominator of eq 14b is negligible. If $K_{BH} > K_{1H}$, then $k_f \gg k_{-d}$ and that term becomes $k_f(k_r + k_{-d})/k_b$; since it is otherwise negligible we assign it this value and obtain eq 14c.

$$k_{BH} = \frac{k_f(k_r + k_{-d})k_a k_d/k_{-a}}{(k_f + k_{-d})(k_r + k_{-d}) + k_b k_{-d}} \quad (14a)$$

$$k_{BH} = \frac{(K_{BH}/K_{1H})(k_r + k_{-d})k_a k_d/k_{-a}}{[(k_f + k_{-d})/k_b](k_r + k_{-d}) + k_{-d}} \quad (14b)$$

$$k_{BH} = \frac{K_{BH}(k_r + k_{-d})k_a k_d/k_{-a}}{K_H(_B k_r + k_{-d}) + K_{1H}k_{-d}} \quad (14c)$$

Two limiting cases for the dependence of k_{BH} on K_{BH} arise, one for strong acids and one for weak acids, relative to **1H**. In the former case ($K_{BH} \gg K_{1H}$; eq 15)

$$k_{BH} = k_a k_d/k_{-a} \qquad K_{BH} \gg K_{1H} \quad (15)$$

the rate will be independent of catalyst acidity ($\alpha = 0$ in eq 7) because the diffusion rate constant k_d differs little for various compounds and is around 10^8–10^{10} M^{-1} sec^{-1} in water.[16] For weak acids ($K_{BH} \ll K_{1H}$; eq 16) the terms in square brackets will all be independent of B structure if it is assumed that B is not interacting with **1H** during its reorganization to products in eq 11 or that $k_{-d} \gg k_r$. Then k_{BH} is simply proportional to K_{BH} and $\alpha = 1$.

$$k_{BH} = K_{BH}[(1 + k_r/k_{-d})(k_a k_d/k_{-a}K_{1H})] \quad (16)$$

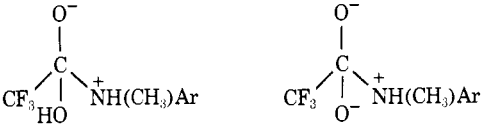
$$K_{BH} \ll K_{1H}$$

Since $\alpha = 1$ throughout the pK_{BH} range of Figure 1, the limit of eq 16 must be in force; this implies that **1H**, the N-protonated tetrahedral intermediate, has pK_a < 5. This is reasonable for an anilinium ion. Therefore the catalyst is completely ionized in the transition state because the proton switch from it to **1** is fast and reversible and the rate-determining step is either diffusion of **1H** and B apart from each other (k_{-d}) or decomposition of **1H** with B still trapped as a spectator within the solvent cage (k_r). If diffusion is rate determining, the anilide nitrogen will bear a full positive charge in the transition state and electron donors will accelerate the reaction. If spectator catalysis prevails, the CN bond is breaking and the positive charge on nitrogen will be smaller, possibly even less than that on the initial-state amide nitrogen; the substituent effect might have either direction.

Therefore, to test for the relative contributions of heavy-atom reorganization (k_r) and diffusion (k_{-d}) processes, we examined the effect of substituents in the anilide ring. Glycine was employed as catalyst. The twofold acceleration by *p*-CH_3 (Table I) shows that (a) diffusion apart (eq 12) is an important rate-determining process for this compound. If the diffusion process of eq 12 were the *only* important route for loss of **1H**, then substitution by *m*-Br would give a sharp decrease in rate. Instead, *m*-Br substitution also increases the rate by about twofold, demonstrating that in its case, heavy-atom reorganization in the solvent cage has become at least a partial rate determinant. The data thus require only the diffusion processes as a rate determinant for the *p*-CH_3 compound, but demand a contribution from reorganization with spectator catalyst present for the *m*-Br compound.

Conclusion

Compound **1H** is formed and decomposes with either diffusion or heavy-atom reorganization (cleavage of the CN bond) in the presence of a spectator catalyst as rate-determining steps, while the proton shifts to and from nitrogen appear to be relatively rapid. Compound **3**, on the other hand, seems to undergo CN



1H **3**

cleavage more rapidly than proton shifts, at least to and from water or its own alkoxide centers, possibly mediated by water as shown by large solvent isotope effects.[6a] This is clearly understandable in terms of the greater driving force furnished by the two alkoxide centers in **3** for breaking the CN bond.

Experimental Section

Materials. Glycine, *N*-glycylglycine, β-alanine, ammonium chloride, trimethylamine, 25% in water (all supplied by Matheson Coleman and Bell), sarcosine (Aldrich Chemical Co. and Nutritional Biochemicals), *n*-butylamine (unknown source, bp 76–77°, lit.[17] 77–78°), L-proline (Calbiochem, A grade), and benzylamine (J. T. Baker) were used without purification. *N*,*N*-Dimethylglycine was also from an unknown source. The amines were converted into their hydrochloride salts by passage of hydrogen chloride gas through an ethanolic solution of the amine or by addition of aqueous hydrogen chloride to the amine–alcohol solution. All hydrochloride salts were recrystallized twice from ethyl alcohol, except *n*-butylamine (recrystallized from ethyl

(17) A. Berg, *Ann. Chim. (Paris)*, *Ser. 7*, **3**, 289 (1894).

acetate); *N*-methylaniline (Matheson Coleman and Bell) was distilled prior to use. *N*-Methyl-2,2,2-trifluoroacetanilide was synthesized from trifluoroacetic anhydride and *N*-methylaniline in ether according to Bourne, Henry, Tatlow, and Tatlow.[18] The substituted anilides were available from previous work.[6a]

Kinetics. Rate constants were determined spectrophotometrically employing a Cary Model 16 (with Sargent recorder, Model SRL) or Beckman DB spectrophotometer. An increase in absorbance (typically 0.2–0.4 absorbance unit) with time was followed at either 285 or 238 nm, the product ultraviolet maxima. Faster reactions were carried out directly in a quartz cuvette secured in a constant-temperature cell holder. Slower reactions were carried out with aliquot sampling from solutions in a 100-ml volumetric flask held in a constant-temperature bath. The data were treated in two ways: for approximately one-half of the runs a Guggenheim procedure[19] was employed in which two sets of an equal number of measurements spaced at a constant time interval were taken, the first set during the first half-life and the second after 3 half-lives. Rate constants for the remaining runs were derived from the points taken during the first half-life and an experimental infinity point. The Guggenheim-calculated rate constant values were approximately 6–8% higher than the infinity point values for the slower glycylglycine runs, due presumably to a small amount of oxidation of *N*-methylaniline which occurred in allowing the solution to stand for the longer times required for the hydrolysis to go to completion (4–5 days). First-order rate coefficients were obtained from a computer calculation of the slope of the least-squares regression line for a plot of $\ln (A - A_t)/(A - A_0)$ *vs.* time. A least-squares program was also applied in the reduction of Guggenheim data.

(18) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, and J. C. Tatlow, *J. Chem. Soc.*, 4014 (1952).
(19) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

pK_a Determination. The pK_a values for the catalyst species were derived from potentiometric titration experiments following the procedure of Albert and Serjeant.[20] Measurements of pH were made with an Instrumentation Labs Digimatic pH meter equipped with a combination silver|silver chloride electrode. The values obtained are included in Table II.

Table II. Ionization Constants of Buffer Species at 25°

	Buffer (BH)	pK_a (μ = 0.05)[a]	pK_a[b]
(1)	*N*-Glycylglycine	8.25 ± 0.01	8.25
(2)	Ammonium	9.24 ± 0.02	9.24
(3)	Benzylammonium	9.41 ± 0.02	9.35
(4)	Glycine	9.70 ± 0.02	9.78
(5)	Trimethylammonium	9.81 ± 0.01	9.80
(6)	*N*,*N*-Dimethylglycine	9.92 ± 0.04	9.94[c]
(7)	Sarcosine	10.04 ± 0.02	9.92[d]
(8)	β-Alanine	10.16 ± 0.02	10.24[c]
(9)	L-Proline	10.54 ± 0.02	10.64
(10)	*n*-Butylammonium	10.62 ± 0.02	10.60

[a] Constant ionic strength maintained by addition of KCl. [b] Literature values of thermodynamic ionization constants from L. Meites, Ed., "Handbook of Analytical Chemistry," McGraw-Hill, New York, N. Y., 1963, pp 1-21, unless otherwise indicated. [c] J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. I, Wiley, New York, N. Y., 1961, p 492. [d] R. C. Weast, Ed., "Handbook of Chemistry and Physics," 50th ed, Chemical Rubber Co., Cleveland, Ohio, 1969–1970, pp 1–118.

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The Methylenimmonium Ion and the Role of Resonance and Inductive Stabilization in Carbonium Ions

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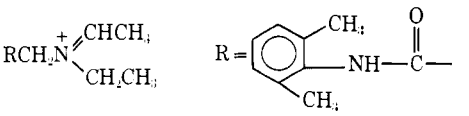
Abstract: The electronic structure and rotational barrier of the methylenimmonium ion and the proton affinity of methylenimine are examined with high quality molecular orbital wave functions. The electronic properties of this resonance stabilized carbonium ion, $CH_2NH_2^+$, are compared with its neutral precursor, CH_2NH, with its neighbors in the periodic table, formaldehyde and protonated formaldehyde, and with methyl, fluoromethyl, and ethyl carbonium ions. CH_2F^+, CH_2OH^+, and $CH_2NH_2^+$ are computed to be resonance stabilized by 31, 48, and 66 kcal/mol, respectively, relative to the methyl cation. The rotational barrier of $CH_2NH_2^+$ is found to be higher than its neutral precursor, CH_2NH. $CH_2NH_2^+$ is also *inductively* stabilized relative to CH_3^+.

The role of resonance in the stabilization of carbonium ions has not as yet been examined quantitatively; the calculations reported here on the methylenimmonium ion and other resonance stabilized carbonium ions will allow us to compare simple carbonium ions, such as ethyl and methyl cation[2] with resonance stabilized ions $CH_2NH_2^+$, CH_2OH^+, and CH_2F^+.

The methylenimmonium ion $(CH_2NH_2)^+$ is a prototype of postulated intermediates in biologically important N-dealkylation reactions. The structure



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