The Timing of the Proton-Transfer Process in Carbonyl Additions and Related Reactions. General-Acid-Catalyzed Hydrolysis of Imines and *N*-Acylimines of Benzophenone[1a]

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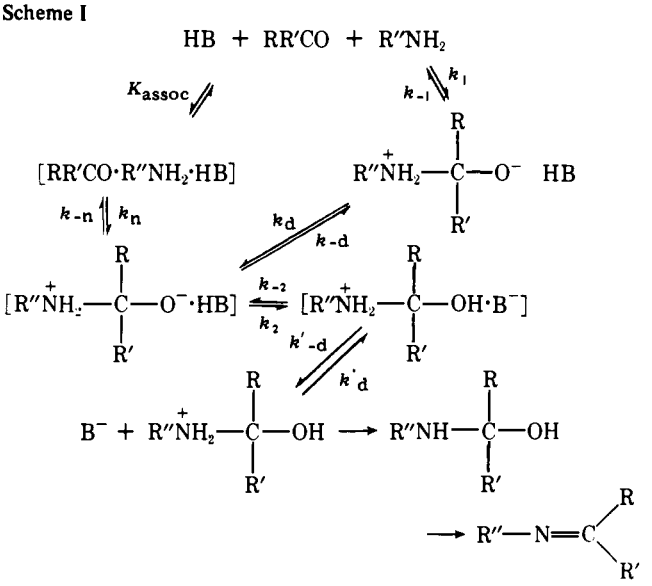
Abstract: Observed general-acid-catalyzed hydrolysis of benzophenone imines, $Ph_2C{=}NR$, or the kinetically equivalent general-base-catalyzed hydrolysis of the conjugate acids $Ph_2C{=}N^+HR$, corresponds mechanistically to general-base-catalyzed amine expulsion from the conjugate acid (T^+) of the tetrahedral intermediate from water addition to $Ph_2C{=}NR$. Brønsted β values for this catalysis by carboxylate and cacodylate ions are 0.96 (for R = H), 0.93 (for R = C_2H_4CN), and 0.76 (for R = CH_2CN). These results, combined with calculations that suggest that amine expulsion from the zwitterionic intermediate, $T^{\pm}$, from ammonia is slower than diffusion processes involving $T^{\pm}$ and catalyst, are consistent with a mechanism in which a *simple* proton transfer process is not rate determining. Because of the stability of $T^{\pm}$ it is unlikely that catalysis in this system is "enforced" by the lifetime of this intermediate. We suggest that catalysis of these reactions is observed because hydrogen bonding of $T^{\pm}$ to the conjugate acid of the catalyst provides an energetic advantage by stabilizing both $T^{\pm}$ and the transition state for amine expulsion from this species. Hydrolysis of *N*-acyl benzophenone imines, $Ph_2C{=}NC(O)CH_2X$ (X = H, OCH_3, or Cl), involves a rapid, favorable equilibrium for addition of water across the C=N bond, followed by amide expulsion from the carbinolamide. The latter process, analogous to amine expulsion from carbinolamines, is subject to weak general acid catalysis with Brønsted α values of 0.5–0.6. This catalysis probably corresponds mechanistically either to (1) bifunctional or "one-encounter" catalysis in which one or both of the proton-transfer processes is "concerted" with C–N cleavage, or (2) general base catalysis of the expulsion of the *O-protonated* amide from $Ph_2C(OH)N^+HC(OH)CH_2X$. For *uncatalyzed* carbinolamide cleavage a cyclic transition state with intramolecular proton transfer to the acyl oxygen is suggested to explain the observed insensitivity to substituents, X, of amide expulsion from the neutral carbinolamides, $Ph_2C(OH)NHC(O)CH_2X$.

Studies of the detailed mechanism and timing of general acid catalysis in carbonyl addition reactions[2-6] have demonstrated the generality of mechanistic Scheme I for the addition of moderately and strongly basic nitrogen nucleophiles to aldehydes (R = H). According to this mechanism a zwitterionic tetrahedral intermediate, $T^{\pm}$, formed in an initial attack step, undergoes a proton transfer to give the neutral intermediate T^0 in a subsequent step or steps that may or may not be kinetically significant, depending on the basicity of the amine and the magnitude of k_{-1}. For strongly basic amines and highly reactive aldehydes such as formaldehyde k_{-1} is small relative to proton-transfer steps, and these steps are not kinetically significant. For less basic amines and substituted benzaldehydes, k_{-1} is comparable to the rate constants for (diffusion controlled) protonation of $T^{\pm}$ and under appropriate conditions these proton-transfer steps are the predominantly rate-determining processes for many such reactions. Further decreases in the basicity of the amine result in C–N bond cleavage becoming even faster than diffusional separation of the encounter complex [$T^{\pm}$·HB]; in these cases the preferred pathway of reaction does not involve free $T^{\pm}$ but instead must proceed via a preassociation mechanism involving nucleophilic attack on the carbonyl group within a termolecular encounter complex. Observed general acid catalysis of these types of reactions corresponds to the processes described by k_n and k_2 in Scheme I.

Scheme I



For some reactions that proceed predominantly via the trapping of free $T^{\pm}$ at pH values of ca. 2–4, a second pathway for hydronium ion catalysis is observed at higher acidity where the rate-determining step for the trapping mechanism is pH-independent attack of the amine on the carbonyl compound.

We have previously observed that a decrease in the electrophilic character of the carbonyl compound favors this alternative pathway, as destabilization of $T^{\pm}$ renders the stepwise pathway increasingly unfavorable. For example, there is no evidence for a stepwise trapping mechanism for the hydronium ion catalyzed addition of semicarbazide to *p*-methoxybenzaldehyde, whereas the analogous reaction of *p*-nitrobenzaldehyde occurs predominantly via the trapping mechanism.[3] For this reaction the alternate pathway is slightly more than an order of magnitude faster than the (hypothetical) reaction via the trapping pathway, and hence is the only experimentally observable pathway. This is a result of the fact that the alternate pathway is very insensitive to polar substituents on the carbonyl compound, whereas the trapping pathway has essentially the same sensitivity to substituents as equilibrium addition of nucleophiles ($\rho \simeq 1.8$).[7] The present investigation was undertaken in an attempt to elucidate in detail this mechanism for acid catalysis of carbinolamine formation from carbonyl compounds of extremely low electrophilicity. The substitution of a second benzene ring for hydrogen lowers the equilibrium constants for addition of various nucleophiles to benzophenone approximately five orders of magnitude relative to benzaldehyde.[8] Based on extrapolation of known structure–reactivity correlations,[2] this should decrease the rate

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Table I. Kinetic Constants for Hydrolysis of Substituted Benzophenone Imines, $Ph_2C{=}NR$[a]

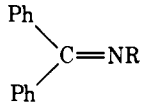
	R = H	R = C_2H_4CN	R = CH_2CN
pK_a	7.0[b]	4.73	2.76
k_h, s^{-1}	1.5×10^{-3} [c]	1.28×10^{-2}	4.6×10^{-1}
$K_h k_e$, s^{-1}	$\leq 3 \times 10^{-5}$	3.0×10^{-3}	4.2×10^{-1}
$K_h k_{OH}$, $M^{-1} s^{-1}$	7×10^8		

[a] At 25 °C, ionic strength 1.0 M (KCl). [b] Reference 9. [c] This value is in good agreement with the literature value of 1.3×10^{-3} s^{-1} determined at ionic strength 0.5 M (ref 9).

constant for a given amine for the alternate pathway by a factor of 10 or less while decreasing $k_d k_l / k_{-l}$ for the trapping pathway by a factor of about 10^5. Hence, even for quite strongly basic amines, for which the trapping pathway is normally favored, we anticipate the alternate pathway for catalysis to predominate with benzophenone.

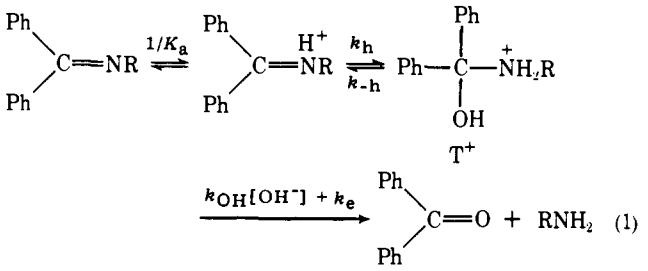
Results

Amine addition to the very poor electrophile benzophenone is most conveniently approached by study of the reverse reaction. In this work we have reinvestigated the hydrolysis[9] of benzophenone imine **1** and have also studied the hydrolysis of



1, R = H
2, R = CH_2CH_2CN
3, R = CH_2CN

the cyano-substituted imines **2** and **3**, in a search for buffer catalysis of these reactions. At zero buffer concentration the mechanism of this reaction is described by eq 1. At low pH,



amine expulsion from the intermediate is the predominantly rate-determining step. Figure 1 shows pH-rate profiles, extrapolated to zero buffer concentration, for hydrolysis of **1–3**. For these imines, the rate law in the absence of external buffers is given by

$$\text{rate} = \frac{k_h K_h (k_{OH}[OH^-] + k_e)}{k_h + K_h (k_{OH}[OH^-] + k_e)} [Ph_2C{=}N^+HR] \quad (2)$$

where $K_h = k_h / k_{-h}$, the equilibrium constant for water addition to the protonated imine. The observed first-order rate constant, k^0, for hydrolysis in the absence of buffers is given by

$$k^0 = \left(\frac{k_h K_h (k_{OH}[OH^-] + k_e)}{k_h + K_h (k_{OH}[OH^-] + k_e)}\right)\left(\frac{[H^+]}{[H^+] + K_a}\right) \quad (3)$$

and values of the experimentally determined kinetic constants are summarized in Table I. For weakly basic imines **2** and **3** at low pH, elimination of the protonated amine from T^+ occurs exclusively via an uncatalyzed (or water-catalyzed) pathway, k_e. Below the pK_a of the protonated imine, eq 3 reduces to

$$k^0 = \frac{k_h K_h k_e}{k_h + K_h k_e} \quad (4)$$

for **2** and **3**. Above the pK_a of the cyanomethylimine **3**, the rate

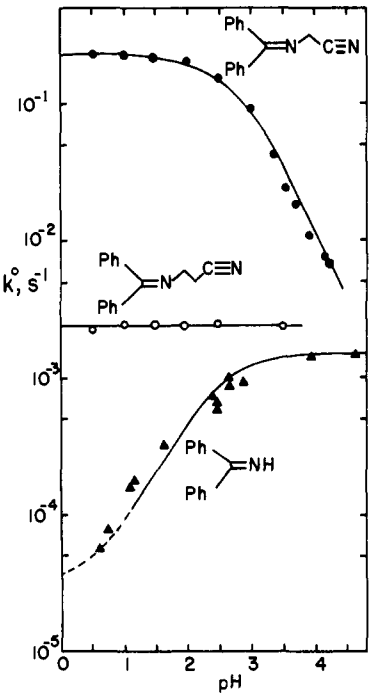


Figure 1. Effect of pH on the rate constants, k^0, extrapolated to zero buffer concentration for hydrolysis of compounds **1–3**. The lines are theoretical curves for the rate constants and pK_a values of Table I. The broken line for unsubstituted benzophenone imine also includes $K_h k_e = 3 \times 10^{-5}$ s^{-1}.

falls off as a result of the decreasing concentration of protonated imine. For the more strongly basic unsubstituted imine **1** the predominantly rate-determining step at pH <2 is elimination of the amine from a neutral (or zwitterionic) transition state (k_{OH}) and the rate for reaction of the fully protonated imine increases with increasing hydroxide ion concentration. There is a small deviation from a slope of 1.0 for the plot of log k^0 (or k_{cor}; see eq 5) vs. pH at the lowest pH values, which may indicate a small contribution of water-catalyzed ammonium ion expulsion from T^+; the curve shown is calculated using an approximate value of 3×10^{-5} s^{-1} for $K_h k_e$. At pH values above 3 the rate-determining step, from the work of Koehler, Sandstrom, and Cordes,[9] is attack of water (k_h) on protonated benzophenone imine.

General Base Catalysis. Expulsion of ammonia and substituted amines from **1–3** is catalyzed by buffers. This catalysis, not previously reported for ammonia expulsion from **1**, is difficult to observe because of partially rate-determining water attack which is presumably negligibly catalyzed by the buffers used at the pH values where catalysis of ammonia expulsion is observable. (An increase of only 0.2% in the rate constant for the water attack step in the presence of 0.7 M cacodylic acid at pH 2.55 is estimated from the effect of cacodylate on the rate of hydrolysis of **1** at pH 5.46.) At pH 2.42 catalysis of the hydrolysis of **1** by a methoxyacetic acid buffer is illustrated in Figure 2. Under these typical conditions, the ratio of rate constants for water and ammonia expulsion from the intermediate is between 0.7 and 1.5, so that neither step is fully rate determining and uncatalyzed attack of water contributes significantly to the observed rate. As a result, experimental rate accelerations by buffer are relatively small, and there is a slight curvature of the plot as rate-determining water attack is more closely approached at high buffer concentrations. Plots of observed rate constants against buffer concentration for **2** and **3** generally show much more marked catalysis at low buffer concentrations and more pronounced curvature at high buffer concentrations. Corrections of observed rate constants for the contribution of uncatalyzed water attack were made according

Table II. General Base Catalysis of Hydrolysis of Substituted Benzophenone Immonium Ions, $Ph_2C{=}NHR^+$ [a]

catalyst	pK_a	concn, M	fraction B^-	fraction $Ph_2C{=}NHR^+$	k_{app}, $M^{-1}\ s^{-1}$ [b]	k^{C^-}, $M^{-1}\ s^{-1}$ [c]
			R = H			
cyanoacetate (1)	2.33[d]	0.05-0.4	0.54	1.0	2×10^{-3}	
		0.05-0.4	0.73	1.0	7×10^{-3}	$6 \pm 3 \times 10^{-3}$
methoxyacetate (3)	3.40[d]	0.05-0.3	0.09	1.0	4.7×10^{-3}	
		0.01-0.25	0.17	1.0	1.04×10^{-2}	5.6×10^{-2}
formate (4)	3.56[d]	0.1-0.6	0.07	1.0	4×10^{-3}	
		0.1-0.6	0.14	1.0	7.8×10^{-3}	5.7×10^{-2}
acetate (5)	4.65[d]	0.05-1.0	4×10^{-3}	1.0	2.3×10^{-3}	0.6
cacodylate (6)	6.15[e]	0.05-0.7	2.5×10^{-4}	1.0	5.4×10^{-3}	21.6
			$R = CH_2CH_2CN$			
chloroacetate (2)	2.74[d]	0.01-0.2	0.51	1.0	4.78×10^{-2}	9.4×10^{-2}
formate (4)	3.56[d]	0.01-0.1	0.20	1.0	0.11	
		0.01-0.1	0.48	1.0	0.16	0.44 ± 0.1
acetate (5)	4.65[d]	0.01-0.1	2.6×10^{-2}	1.0	0.12	
		0.01-0.1	4.8×10^{-2}	1.0	0.2	
		0.01-0.6	9.5×10^{-2}	1.0	0.44	4.5
cacodylate (6)	6.15[e]	0.01-0.1	9.3×10^{-4}	1.0	0.14	
		0.01-0.1	2.6×10^{-3}	1.0	0.29	130 ± 20
			$R = CH_2CN$			
cyanoacetate (1)	2.33[d]	0.01-0.15	0.78	0.43	2.36	
		0.005-0.2	0.88	0.28	2.6	8.9 ± 1.8
chloroacetate (2)	2.74[d]	0.01-0.15	0.48	0.55	5.1	
		0.01-0.15	0.81	0.22	1.3	13 ± 6
formate (4)	3.56[d]	0.01-0.15	0.50	0.14	2.3	
		0.01-0.20	0.80	3.8×10^{-2}	1.8	47 ± 13
acetate (5)	4.65[d]	0.005-0.2	0.17	5.8×10^{-2}	3.8	
		0.005-0.2	0.26	3.5×10^{-2}	2.7	340 ± 40
cacodylate (6)	6.15[e]	0.005-0.5	3.5×10^{-2}	0.10	2.35	6500

[a] At 25 °C, ionic strength 1.0 M (KCl). [b] Slope of a plot of k_{cor} (see text) vs. total buffer concentration. [c] Catalytic constant (average value) in terms of the conjugate base of the catalyst and the conjugate acid of the imine (eq 6). [d] Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353. [e] Reference 14.

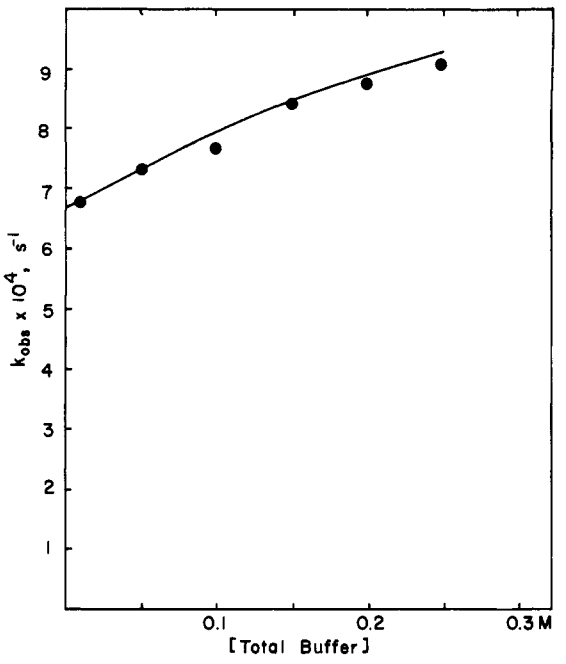


Figure 2. Effect of methoxyacetic acid-potassium methoxyacetate buffer, pH 2.42 (9% anion), on the observed rate constants for hydrolysis of **1**. The line is based on $k^{C^-} = 5.6 \times 10^{-2}\ M^{-1}\ s^{-1}$, $k_h = 1.5 \times 10^{-3}\ s^{-1}$, and an apparent rate constant, $k_h K_h k_{OH}[OH^-]/(k_h + K_h k_{OH}[OH^-])$, of $6.7 \times 10^{-4}\ s^{-1}$ at zero buffer concentration.

to the equation

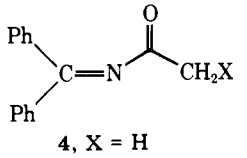
$$k_{cor} = k_{obsd}/(1 - k_{obsd}/k_\infty) \qquad (5)$$

where k_∞, the limiting rate constant for imine hydration, is given by $k_h[H^+]/([H^+] + K_a)$; for **1** and **2** in the pH range studied, k_∞ is equal to k_h. Catalytic constants, k^{C^-}, for ammonium ion explusion from T^+ catalyzed by the conjugate bases of buffers (as defined by eq 6)

$$k_{cor}[Ph_2C{=}NR]_{total} = (k^w_{cor} + k^{C^-}[B^-])[Ph_2C{=}NHR^+] \qquad (6)$$

were determined by dividing the slopes of plots of k_{cor} vs. total buffer concentration by the mole fractions of protonated imine and of buffer conjugate base. Values of k^{C^-} are summarized in Table II.

Benzophenone *N*-Acylimines. We are also interested in the effects of *large* perturbations of the pK_a of the departing nitrogen compound on the characteristics of the catalyzed reaction, and the introduction of an acyl group on nitrogen in compounds **4–6**, which converts the amino component of T^0



4, X = H
5, X = OCH_3
6, X = Cl

to an extremely weakly basic amide moiety, provides one means of producing such a large change in reactivity. Upon addition of **4, 5,** or **6** to aqueous buffer solutions there is a rapid decrease in the absorbance of the initial compound at 260 nm to a value near zero, which is followed by a much slower absorbance increase at the same wavelength.

Hydrolysis of **4, 5,** and **6** in acid solution gives benzophenone (identified by thin layer chromatography). In addition, acid hydrolysis of **4** and **6** gives the corresponding amides; because

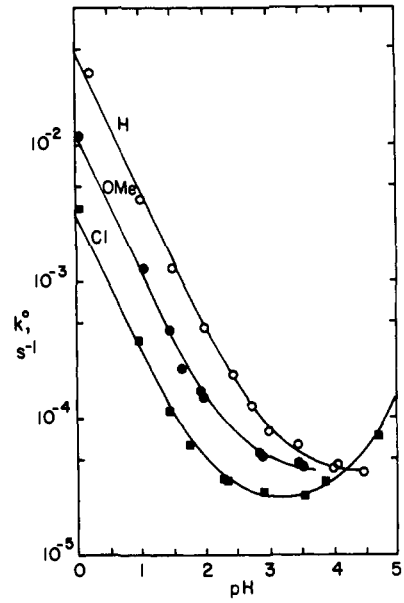


Figure 3. Effect of pH on the rate constants, k^0, extrapolated to zero buffer concentration, for amide expulsion from the carbinolamides derived from **4** (○), **5** (●), and **6** (■). The lines are theoretical curves for the rate constants of Table III, including $k_1^{OH^-} = 1.2 \times 10^5\ M^{-1}\ s^{-1}$ for **6**.

Table III. Kinetic Constants for Hydrolysis of Benzophenone *N*-Acylimines, $Ph_2C{=}NC(O)CH_2X$[a]

	X = H	X = OCH_3	X = Cl[b]
k_1^0, s^{-1}	4.0×10^{-5}	4.0×10^{-5}	2.3×10^{-5}
k_1^H, $M^{-1}\ s^{-1}$	4.6×10^{-2}	1.2×10^{-2}	3.0×10^{-3}

[a] At 25 °C, ionic strength 1.0 M (KCl). [b] A hydroxide ion catalyzed reaction is also observed for this compound above pH 3.5, $k_1^{OH} \sim 1.2 \times 10^5\ M^{-1}\ s^{-1}$.

of the structural and kinetic similarity of **5** to **4** and **6** the products of this reaction were not investigated further. Amide formation precludes the possibility that initial attack of water occurs at the acyl, rather than the imino, carbon of *N*-acylimines. The observed initial absorbance decrease in water is most reasonably explained by a favorable equilibrium for nucleophilic addition to the imino group. *N*-Acylimines react readily with alcohols and amines form adducts at the imino carbon;[10] the observed absorbance changes in aqueous solution provide evidence that the analogous reaction with water occurs prior to amide expulsion. The slow subsequent absorbance increase, which is attributed to formation of benzophenone from the carbinolamides, permits direct determination of rate constants for amide expulsion from the carbinolamides. In acidic solution this reaction proceeds via a hydronium ion catalyzed and an uncatalyzed pathway (eq 7). The pH-rate profiles for hydrolysis of **4–6** are shown in Figure 3, and the rate constants k_1^0 and k_1^H are given in Table III.

$$\text{rate} = (k_1^0 + k_1^H[H^+])[Ph_2C(OH)NHC(O)CH_2X] \quad (7)$$

The hydrolysis of *N*-acylimines is subject to weak buffer catalysis (Table IV); depending on the compound, only general acid catalysis (k^{CH}) or both general acid and general base catalysis are observed. Observed accelerations by 1.0 M buffers are about 10–30% of the base-line rate (Figure 4). That these represent (at least in part) true catalysis and not a solvent or medium effect of the buffer acids is strongly suggested by the lack of any significant effect of formamide or acetamide on the rates for hydrolysis of **4** and effects of these additives on the hydrolysis of **5** and **6** that are smaller than the effects of comparable concentrations of carboxylic acids (Table V and Figure 4B). Estimates of catalytic constants for buffer acids with **5** and **6** were obtained after correction of the observed slopes of plots of rate constant vs. buffer concentration for this "medium effect" acceleration by the conjugate acid using the appropriate amide as a model.[11] The effect of amides (especially acetamide) on the rate of hydrolysis of **6** is large enough to cast doubt on the quantitative interpretation of the "catalytic" constants for some buffer acids with **6**, although even in the most ambiguous case observed the difference in the rate accelerations caused by 1.0 M acetamide and acetic acid (Figure 4B) is not inconsistent with a *small* amount of true acid catalysis.

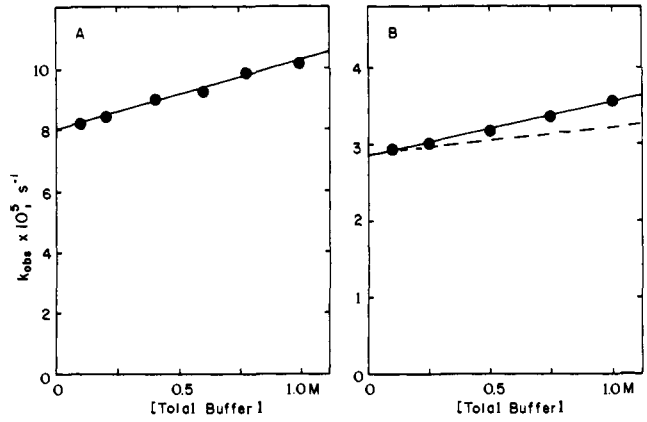


Figure 4. Buffer catalysis of hydrolysis of *N*-acylimines: curve A, **4** plus methoxyacetic acid-potassium methoxyacetate (72% acid); curve B, **6** plus acetic acid-potassium acetate (98% acid), pH 2.88. The broken line in graph B represents the effect of acetamide on the base-line rate of hydrolysis of **6**, determined from the data of Table V.

The evidence for general acid catalysis of *N*-acylimine hydrolysis by stronger acids, namely, cyanoacetic, methoxyacetic, and formic, is much better. We conclude that these reactions are general acid catalyzed, although experimental uncertainties, which are unavoidable because of the very small rate accelerations involved, preclude accurate quantitative determination of catalytic constants in many cases.

Discussion

Under conditions where the expulsion of the amine from the tetrahedral addition intermediate is rate determining, the hydrolysis of benzophenone imine and related compounds with electron-withdrawing alkyl substituents on nitrogen is catalyzed by carboxylic and cacodylic acid buffers. It is of interest that we are able to observe buffer catalysis of the hydrolysis of **1** which corresponds, in the reverse direction, to catalysis of attack of the relatively strong base, ammonia, upon benzophenone; general catalysis of attack of strongly basic amines on more reactive carbonyl compounds is not commonly observed.[5,12]

For the reactions of *protonated* imines, this catalysis is kinetic general base catalysis and follows the rate law of eq 6. Slopes of Brønsted plots (Figure 5) of the logarithms of the observed catalytic constants, k^{C^-}, against pK_a for carboxylate and cacodylate ion ctalysts are 0.96 for leaving ammonia ($pK_a = 9.49$),[13] 0.93 for cyanoethylamine ($pK_a = 8.2$),[14] and 0.76 for cyanomethylamine ($pK_a = 5.48$). Corresponding β values calculated including water as a catalyst in the correlation are 1.0, 0.84, and 0.78 for ammonia, cyanoethyl-, and cyanomethylamine, respectively. Although these values are large, at least one of them is significantly smaller than 1.0. There is no evidence for any break in these Brønsted plots with increasing basicity of the catalyst.

From the rate law for the reaction the observed catalysis must involve a transition state with zero net charge. Kinetically equivalent mechanisms consistent with such a transition state

Table IV. General Acid Catalysis of Hydrolysis of Benzophenone *N*-Acylimines, $Ph_2C{=}NC(O)CH_2X$[a]

catalyst	pK_a	concn, M	fraction BH	k_{app}, $M^{-1}\,s^{-1}$ [b]	k^{CH}, $M^{-1}\,s^{-1}$ [c]
			4, X = H		
chloroacetic acid	2.74[d]	0.1-0.6	0.73	6.8×10^{-5}	
		0.1-0.6	0.83	6.0×10^{-5}	$(8 \pm 1) \times 10^{-5}$ [e]
methoxyacetic acid	3.40[d]	0.1-1.0	0.72	2.3×10^{-5}	
		0.1-1.0	0.90	4.6×10^{-5}	$(4 \pm 1) \times 10^{-5}$
formic acid	3.56[d]	0.1-0.6	0.77	2.6×10^{-5}	
		0.1-0.5	0.88	2.2×10^{-5}	$(2.5 \pm 0.8) \times 10^{-5}$ [j]
β-hydroxypropionic acid	4.35[f]	0.1-0.8	0.50	7×10^{-6}	
		0.1-0.8	0.61	5×10^{-6}	$\leq 1.1 \times 10^{-5}$ [j]
acetic acid	4.65[d]	0.1-0.6	0.59	$(8.4 \pm 0.2) \times 10^{-6}$	
		0.1-0.5	0.79	1.5×10^{-5}	
		0.1-1.0	0.82	$(8 \pm 5) \times 10^{-6}$	
		0.1-1.0	0.94	$\leq 1.5 \times 10^{-5}$	$\leq 1.6 \times 10^{-5}$ [j]
cacodylic acid	6.15[g]	0.2-1.0	1.0	$\leq 7.5 \times 10^{-6}$ [h]	$\leq 7.5 \times 10^{-6}$
			5, X = OCH_3		
cyanoacetic acid	2.33[d]	0.1-1.0	0.68	3×10^{-5}	
		0.1-1.0	0.82	6.5×10^{-5}	$(6 \pm 2) \times 10^{-5}$
formic acid	3.56[d]	0.1-1.0	0.50	1.1×10^{-5} [i]	
		0.1-1.0	0.80	1.3×10^{-5} [i]	$(1.4 \pm 0.4) \times 10^{-5}$ [j]
acetic acid	4.65[d]	0.1-1.0	0.50	$\leq 10^{-6}$	
		0.1-1.0	0.94	6.0×10^{-6} [i]	
		0.1-1.0	0.98	3.6×10^{-6} [i]	$(5 \pm 2) \times 10^{-6}$
			6, X = Cl		
cyanoacetic acid	2.33[d]	0.1-1.0	0.52	7×10^{-6} [i]	
		0.1-1.0	0.80	1.2×10^{-6} [i]	$(1.6 \pm 0.2) \times 10^{-5}$
formic acid	3.56[d]	0.1-1.0	0.50	6.2×10^{-6} [i]	
		0.1-1.0	0.82	3.8×10^{-6} [i]	
		0.1-1.0	0.93	2.4×10^{-6} [i]	2.5×10^{-6} [k]
acetic acid	4.65[d]	0.1-1.0	0.48	1.6×10^{-5} [i]	
		0.1-1.0	0.85	7.3×10^{-6} [i]	
		0.1-1.0	0.98	3.4×10^{-6} [i]	$\sim 3 \times 10^{-6}$ [k]

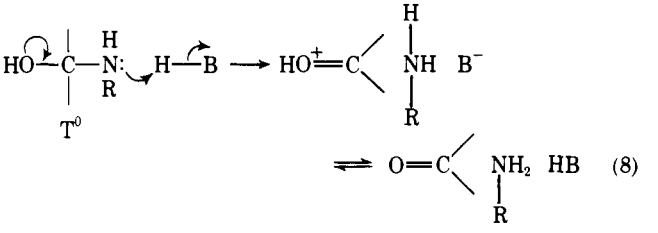
[a] At 25 °C, ionic strength 1.0 M (KCl). [b] Slope of a plot of observed rate constant vs. total buffer concentration, unless otherwise noted. [c] Catalytic constant for the conjugate acid of the catalyst (average value). [d] Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353. [e] Average value of (k_{app}/fraction BH); the absence of general base catalysis by the anion was assumed since such catalysis is not observed with methoxyacetate anion. [f] Determined by potentiometric titration (this work). [g] Reference 14. [h] Based on the observation of no rate acceleration in this experiment (at pH 3.0) and the assumption that a 10% increase in rate would have been detectable. [i] Slope of k_{obsd} vs. total buffer concentration, corrected for the "medium effect" of the un-ionized acid (see text and Table V). [j] Upper limit is based on the assumption that there is no general base catalysis by the anion; lower limit is the intercept at 1.0 of a plot of k_{app} against mole fraction of conjugate acid. [k] Intercept at 1.0 of a plot of k_{app} against mole fraction of conjugate acid.

Table V. "Medium" Effect of Additives on k^0_{obsd} for Hydrolysis of Benzophenone *N*-Acylimines, $Ph_2C{=}NC(O)CH_2X$[a]

compd (X)	additive	pH	concn, M	k_{obsd}/k^0_{obsd}
4 (H)	chloroacetic acid	0.98[b]	0.5	1.03
			1.0	1.04
	formamide	3.12	0.5	1.01
			1.0	1.03
	acetamide	3.09	0.5	0.99
			1.0	0.96
		4.02	0.5	1.01
			0.75	0.99
5 (OCH_3)	cyanoacetic acid	0.51[b]	1.0	0.95
	formamide	2.82	1.0	0.97
	acetamide	2.82	1.0	1.08
6 (Cl)	cyanoacetamide	1.62	0.3	0.99
			0.6	0.95
		2.18	0.3	1.08
			0.6	1.09
	formamide	2.94	1.0	1.06
	acetamide	2.94	1.0	1.13

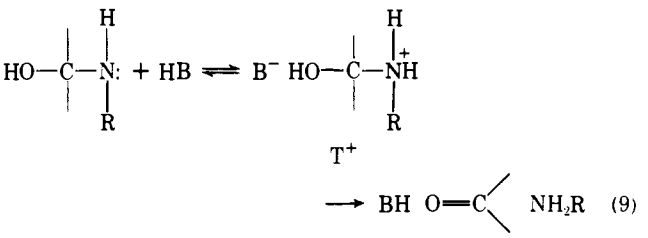
[a] At 25 °C, ionic strength 1.0 M (KCl). [b] Calculated k_{obsd}/k^0_{obsd} = 1.01 at this pH based on observed catalysis at higher pH values.

involve either protonation of T^0 at nitrogen by an acid or deprotonation of T^+ at oxygen by its conjugate base. We favor a mechanism involving oxygen as the site of the catalysis for the following reasons. (1) "*Concerted*" general acid catalysis (eq 8) by protonation at nitrogen is unlikely, since catalysis is



(8)

observed by acids whose pK_a values are below those expected[15] for nitrogen of the intermediates T^+ derived from ammonia or cyanoethylamine, and are close to the estimated pK_a of 1.8 for the cyanomethylamine adduct. Hence there would be little or no driving force for the transfer of a proton from attacking nitrogen in the transition state for the reverse reaction, and general catalysis of this type is not predicted.[19] (2) Rate-determining *simple* protonation of T^0 should give Brønsted plots[20] with a break between slopes of $\alpha = 0$ ($\beta = 1$) and $\alpha = 1$ ($\beta = 0$) at a pK_a value corresponding to the pK_a of T^+. The estimated pK_a values of T^+ species derived from **2** and **3** are 4.5 and 1.8, respectively, and lie within the range of the series of catalysts in Figure 5; yet no evidence for a break is observed. Furthermore, the slope, β, of 0.76 for **3** corresponds to an unreasonable α value of 0.24 for a proton transfer that is thermodynamically unfavorable for most of the acids studied and hence should have $\alpha = 1.0$. We conclude that the most reasonable mechanism for catalysis of carbinolamine cleavage in the benzophenone imine series is specific acid-general base



catalysis (eq 9) and involves the same site as the more extensively investigated reactions[2-6] of weakly acidic nitrogen nucleophiles with aldehydes (Scheme I).

For the reaction of **3** the observed β value of 0.76 is significantly less than unity, and hence this reaction, unlike that of many aldehyde derivatives of weakly basic amines, must not involve a rate-determining *simple*, thermodynamically unfavorable proton transfer from T^+ to the base catalyst. For **1** and **2** the observed β values are larger and are not inconsistent with a rate-determining simple proton transfer. However, for such a process to be rate determining, the breakdown of $T^{\pm}$ (k_{-1}, Scheme I) must occur at a rate comparable to that for encounter of $T^{\pm}$ with a catalyst molecule (k_d[HB]). Arguments to be presented below strongly suggest that C-N cleavage of $T^{\pm}$ derived from **1** is much slower than the diffusion-controlled encounter of this species with a molecule of HB at the low pH values and relatively high buffer concentrations (see Table II) employed in this study. Hence we conclude that the rate-determining step for this reaction is also not a *simple*, diffusion-controlled proton transfer.

The magnitude of the observed β values ($\geq$0.76) suggests a highly unsymmetrical transition state in which proton transfer to the base is far advanced, but there is still some interaction between the anionic oxygen and the proton. This corresponds, in the reverse direction, to a mechanism for amine attack on benzophenone with α values for general acid catalysis between 0.04 and 0.24, and only a small extent of proton transfer from general acid catalysts to the carbonyl oxygen. These α values are consistent with a transition state in which the role of the catalyst is to provide stabilization of a developing negative change by hydrogen bonding. Similar α values of 0.13-0.26 and $-\partial\alpha/\partial pK_{RSH}$ of 0.026 have been observed for hydrogen-bonding catalysis of thiol anion attack on acetaldehyde.[21] The limited data available for the present reaction series suggests that there may be a similar small decrease in α with increasing amine basicity, with an approximate value of $-\partial\alpha/\partial pK_{RNH_3^+} = 0.05$.

Hydrogen-bonding mechanisms of catalysis for cleavage of T^+ are possible if (1) the intermediate $T^{\pm}$ derived from complete proton transfer is so unstable that C-N bond cleavage occurs faster than diffusional separation of $T^{\pm}$ and the catalyst ("enforced catalysis")[22] or (2) hydrogen bonding decreases the energy of the transition state enough to offset the disadvantage with respect to C-N cleavage of a hydrogen-bonded transition state with some attenuation of the negative charge on oxygen, relative to $T^{\pm}$ in which a full negative charge provides the driving force for amine expulsion. Estimates of the stability of $T^{\pm}$ derived from benzophenone and the amines in this investigation suggest that hydrogen-bonding catalysis in this system is not "enforced". Based on an extrapolation of structure-reactivity correlations (see below) for similar compounds, we estimate k_{-1} (Scheme I) for $T^{\pm}$ derived from ammonia and benzophenone to be 10^6-10^7 s^{-1}; i.e., this hypothetical intermediate must be long-lived enough to be able to undergo diffusional separation from the catalyst prior to C-N bond breaking.

(1) Log k_{-1} for expulsion of methoxyamine from **7** is estimated[2] to be 8.46. The effects on k_{-1} of the structural changes involved in conversion of **7** to **8** are estimated as follows. Substitution of benzaldehyde for *p*-chlorobenzaldehyde decreases

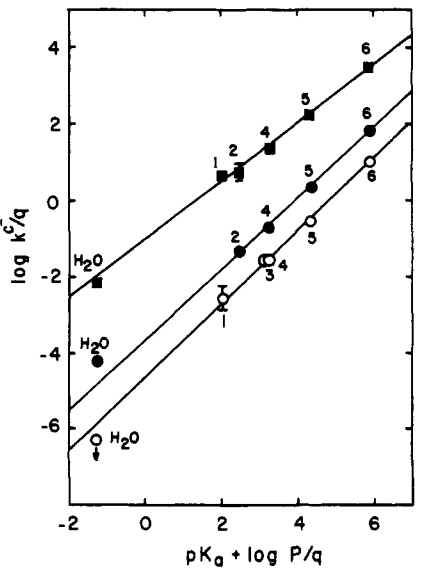
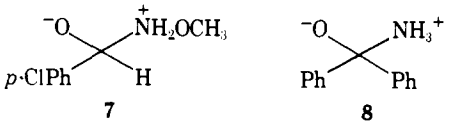


Figure 5. Brønsted plots for general base catalysis of the hydrolysis of protonated **1** (○), **2** (●), and **3** (■), under conditions of rate-limiting amine expulsion from the tetrahedral intermediate. Statistical corrections were made according to the procedure of Bell, R. P.; Evans, P. G. *Proc. R. Soc. London, Ser. A* **1966**, *291*, 297. Catalysts are identified in Table II. Least-squares slopes of the lines for carboxylate and cacodylate ion catalysis are 0.96 for **1** (cyanoacetate omitted from correlation), 0.93 for **2**, and 0.76 for **3**. The points for water catalysis were not used in calculation of the slopes shown.



7 **8**

log K_{ad} for neutral carbinolamine formation by −0.17 (using $\rho^+ = 1.5$)[3,7] and substitution of benzophenone for benzaldehyde gives an additional Δ log K_{ad} of approximately −4.86,[8] for an overall Δ log K_{ad} of −5.0. If k_{-1} is 0.2 times as sensitive as K_{ad} to carbonyl substituents,[2] substituting benzophenone for *p*-chlorobenzaldehyde should hence increase log k_{-1} by *~1.0 unit*. Substitution of methoxyamine (log K_{ad} = 1.13 for addition to *p*-chlorobenzaldehyde)[2] by ammonia decreases K_{ad} by a factor Δ log $K_{ad} = \Delta\gamma = -1.1$, assuming γ for ammonia to be similar to that for aliphatic amines.[23] Values of log k_{-1} of 8.46 and ~10.34 for expulsion of methoxyamine[2] and acethydrazide,[6] respectively, from the *p*-chlorobenzaldehyde adducts suggest that k_{-1} is ~0.8 as sensitive to amine substituents as the experimental quantity[3] ($0.8\Delta pK_a + \Delta$ log K_{ad}). Using this relationship, Δ log k_{-1} upon substitution of ammonia for methoxyamine is $-0.8[0.8(4.76) - 1.1]$ or −2.2. The predicted value for log k_{-1} is thus 8.46 + 1.0 − 2.2 or *7.3*. (2) Alternatively, trimethylamine may be used as a model for ammonia. The expulsion of trimethylamine from a zwitterionic formaldehyde adduct[24] has a rate constant of 3.4×10^3 s^{-1}. Substitution of benzophenone for formaldehyde[8] gives Δ log $K_{ad} \sim -12$. If it is again assumed that k_{-1} is 0.2 times as sensitive as K_{ad} to carbonyl substituents, one obtains log k_{-1} = *5.9*.

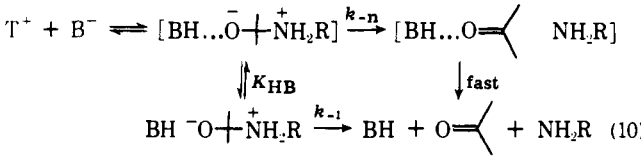
These estimates are obviously not highly accurate because of the long extrapolations needed to compare benzophenone with the much more reactive aldehydes, but they indicate that the intermediate $T^{\pm}$ derived from ammonia is almost certainly not too unstable to exist. In fact k_{-1} is not extraordinarily fast, and catalysis of this reaction at low pH and high buffer concentrations is very unlikely to be "enforced" by a lifetime of $T^{\pm}$ that is shorter than the time required for transport processes in solution.

For the less basic cyanoethyl- and cyanomethylamine ad-

ducts, values of log k_{-1} are 7.4 ± 0.7 and 9.2 ± 0.7, respectively, based on the assumption that log k_{-1} is (0.8)(0.8) or 0.64 as sensitive to amine substituents as the pK_a of the amine. The calculated range for k_{-1} and the observed β value of <1.0 for the cyanomethylamine adduct require that, if catalysis of this reaction is "enforced", it must involve a hydrogen-bonding preassociation mechanism with k_{-d} (Scheme I) less than 10^9–10^{10} s^{-1}. Estimates of k_{-d} for similar hydrogen-bonded complexes derived from an acid catalyst and the acethydrazide adduct of *p*-chlorobenzaldehyde[6] are $10^{9.5}$–10^{10} s^{-1}. Hence, it is possible that the observed catalysis of this reaction is also not "enforced" by a lifetime of $T^{\pm}$ that is shorter than the time required for separation of the complex [$T^{\pm}$···HB], although the case for nonenforced catalysis of this reaction is weaker than that for the corresponding reaction of the ammonia derivative.

Nonenforced catalysis by hydrogen bonding appears to be quite rare, although it has been established as the mechanism for general-base-catalyzed cleavage of a carbonyl bisulfite adduct[25] and as one mechanism for general-base-catalyzed expulsion of a moderately basic thiol anion from an acetaldehyde hemithioacetal.[21] A related mechanism, in which O–H and C–N bond cleavage processes are *concerted*, although $T^{\pm}$ is probably not too unstable to exist, has been suggested for general base catalysis of aniline elimination from T^{+} derived from maleanilic acids.[26]

Hydrogen-bonding catalysis provides a lower energy pathway than reaction via free $T^{\pm}$ in carbonyl–amine reactions where C–N bond cleavage is relatively difficult, if there is significant stabilization of $T^{\pm}$, and of the transition state for its formation from reactants, by hydrogen bonding to the catalyst. This stabilization of $T^{\pm}$ and the consequent increase in its concentration must be greater than any retardation of amine expulsion from hydrogen-bonded [$T^{\pm}$···HB] relative to that from the presumably more reactive free $T^{\pm}$. For the mechanism of eq 10 the upper pathway involving C–N cleav-

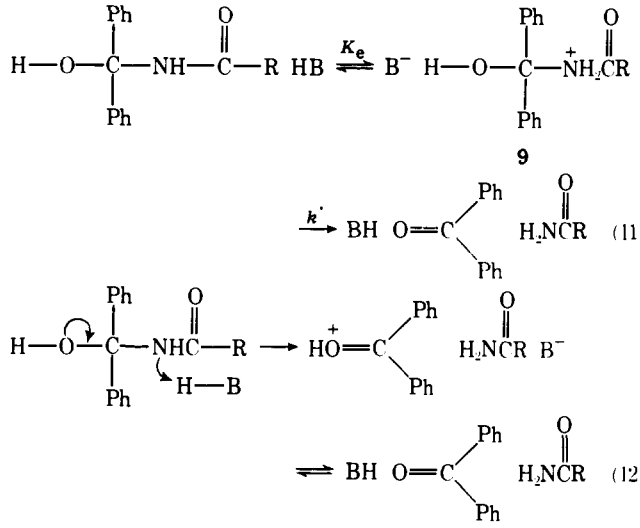


(10)

age within the hydrogen-bonded complex is energetically favorable when $K_{HB} > k_{-1}/k_{-n}$. This is possible if there is significant stabilization of the hydrogen-bonded complex ($K_{HB} > 1$) and if the transition state for C–N cleavage is not very sensitive to the negative charge density on oxygen; i.e., if there is little donation of negative charge from oxygen into the developing double bond in the transition state. The latter condition will be fulfilled if the transition state is relatively "early", with little C–N cleavage, and/or if rehybridization of carbon has not occurred to a significant extent in the transition state. It should be noted that the existence of nonenforced catalysis by hydrogen bonding does not require that the hydrogen-bonded transition state be lower in energy than the intermediate $T^{\pm}$ itself, but only that this transition state be lower than the corresponding *transition state* (for k_1 and k_{-1}) involving free $T^{\pm}$. It is unnecessary to assume any unusual effects of hydrogen bonding on the transition state for k_{-n} that are not also manifested in similar hydrogen bonding that stabilizes $T^{\pm}$.

Benzophenone *N*-Acylimines. The hydrolysis of benzophenone *N*-acylimines **4–6** involves rapid preequilibrium formation of the carbinolamide[10] which is followed by amide expulsion. The observation that the absorbance at 260 nm decreases to near zero before the onset of the second phase of reaction indicates that there is essentially complete conversion of **4–6** to carbinolamides and the observed rate constants thus correspond directly to intermediate breakdown. At low pH, in addition to an uncatalyzed mechanism of reaction, there is a reaction pathway that is catalyzed by hydronium ion and also (weakly) by carboxylic acids. Brønsted plots for catalysis by hydronium ion and carboxylic acids (not shown) have slopes, α, 0.5–0.6. Because of the very small values of catalytic constants for carboxylic acids the accuracy of the Brønsted plots is insufficient to provide evidence for any change in slope with structural variations of the amide leaving group. Increasing electron withdrawal by the amide substituent decreases the rate of the acid-catalyzed reaction: the slope of a plot of log k_1^H for hydronium ion catalysis against the pK_a of the parent carboxylic acid of the amide leaving group is 0.63.

By analogy to mechanisms for expulsion of simple amines from tetrahedral intermediates, two kinetically indistinguishable mechanisms are possible for acid-catalyzed breakdown of carbinolamides, namely, specific acid–general base catalysis (eq 11), the mechanism assigned above for aliphatic amines and ammonia, and true general acid catalysis (eq 12).



(11)

(12)

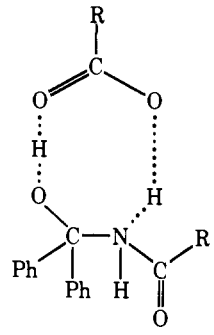
We believe that neither mechanism in its simplest form provides a reasonable explanation for general acid catalysis of carbinolamide cleavage. The estimated equilibrium constants for formation of intermediate **9** and the absolute magnitude of observed rate constants for carbinolamide breakdown are not consistent with the intermediacy of this highly unstable N-protonated amide. The pK_a for **9** when R = CH_3 is estimated to be −11.5 from a pK_a of −7.7 ± 0.1 for N-protonated *N*-methylacetamide,[27] and a ΔpK of −3.8 upon substitution of two phenyl groups (σ_1 = 0.1)[17] and a hydroxyl group (σ_I = 0.25) for H on the nitrogen substituent is estimated using ρ_I = 8.4 for the pK_as of simple ammonium ions.[16] For methoxyacetic acid catalysis, the equilibrium constant, K_e, in eq 11 is thus $10^{-14.9}$, and since for this mechanism the observed catalytic constant $k^{CH} = K_e k'$, k' would have to be approximately 3×10^{10} M^{-1} s^{-1} to account for the observed rate constant of 4×10^{-5} M^{-1} s^{-1}. Hence, simple general-base-catalyzed breakdown of a free N-protonated intermediate would require a rate at least as fast as a diffusion-controlled reaction, and is inconsistent with the observed Brønsted α value of ~0.5–0.6.

The alternative mechanism of eq 12 is rendered unattractive by the following consideration. The mechanism shown would correspond to a Brønsted β value of zero for general base catalysis (at oxygen) of expulsion of a partially protonated amide. Using $\partial\beta/\partial pK_{RNH_3^+} = 0.05$ (see above), a β value of zero corresponds to a leaving group pK_a of approximately −10. *Complete* protonation at nitrogen would give leaving groups with pK_a values of approximately −9, and the observed α value of 0.5 suggests that this protonation is nowhere near complete in the transition state, so that the effective pK_a of the partly

protonated leaving group should be considerably larger. We conclude that a partially protonated amide is probably not a good enough leaving group to be expelled from the intermediate without the added driving force of some negative charge development on oxygen, and hence the mechanism of eq 12 for general acid catalysis, although not rigorously excluded, is unlikely.

Two alternative mechanisms that are consistent with the experimental observations are (a) bifunctional or "one-encounter" catalysis and (b) general base catalysis of expulsion of *O-protonated* amide.

(a) Bifunctional catalysis by carboxylic acids has been proposed for a number of reactions involving expulsion of nitrogen-containing leaving groups from tetrahedral intermediates.[28] Frequently this catalysis is a result of the ability of the base, generated in a diffusion-controlled general-acid-catalyzed process, to abstract a proton from T^+ prior to diffusional separation of $[T^+\cdots B]$. Our observed results are consistent with a one-encounter or bifunctional catalytic mechanism for carboxylic acids (transition state **10**) in which the



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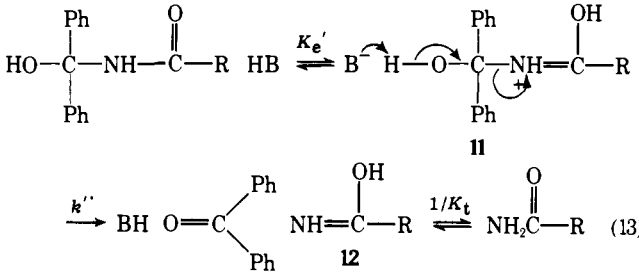
rate-determining step is a rapid proton transfer from the oxygen of initially formed N-protonated carbinolamide, *concerted* with C-N breaking, within a complex of carboxylate anion and T^+. This mechanism requires a rate constant greater than 10^{10} s^{-1} for the reaction within the complex $[T^+\cdots B]$ and is hence not consistent with simple proton transfer from the oxygen of T^+ to the carboxylate anion, which is thermodynamically unfavorable and should hence not be extraordinarily fast. Alternatively *both* proton transfers may be in some sense concerted with the C-N bond breaking process.



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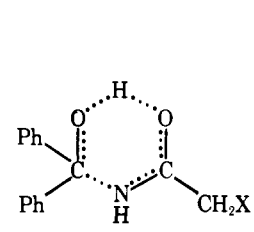
12 (13)

(b) A mechanism (eq 13) that involves protonation of the carbinolamide at the acyl oxygen is also consistent with the absolute magnitudes of the rate constants. The pK_a for O-protonated *N*-methylacetamide[29] is approximately −1.2. If it is assumed that O-protonation is about 0.3 times as sensitive to N substituents as N-protonation,[30] the O-protonated intermediate (**11**) should have a pK_a of $-1.2 - [0.3(3.8)]$ or about −2.3, and the equilibrium concentration of **11** would be about nine orders of magnitude greater than that of **9**, more than adequate to account for the observed reaction rate. The mechanism of eq 13 implies that in the reverse direction the amide undergoes an unfavorable tautomerization prior to nucleophilic attack on the carbonyl group. This mechanism can still provide an energetically favorable reaction pathway if the higher pK_a and greater nucleophilicity of the imido tautomer **12** are large enough to offset the unfavorable equilibrium ($K_T = 10^{-8}$ for *N*-methylacetamide[27]) for tautomerization. In the case of acetamide this is possible if β_{nuc} is ≥ 0.5 since the ΔpK for N-protonated acetamide and its imido tautomer **12** is ca. 15, based on the assumption that the pK_a of N-protonated **12** is similar to that of an imido ester.

According to the mechanism of eq 13 the experimental α values for general acid catalysis correspond to β values of 0.4–0.5 for general base catalysis of imidate expulsion from **11**. Since the pK of departing unsubstituted acetimidate is probably near 7, the magnitude of the β value for this reaction is unexpectedly small based on our observation of much larger β values for base catalysis of the corresponding reactions of moderately basic aliphatic amines. This apparent inconsistency may result from large differences in structure and charge delocalization between the amine and imidate leaving groups.

Amide expulsion from *N*-acylimines also proceeds via an uncatalyzed (or water-catalyzed) pathway. For this reaction the observed rate constants show little dependence on polar substituents on the amide moiety: a plot of log k_1^0 vs. the pK_as of the carboxylic acids corresponding to the amide leaving groups has a slope of about +0.13. This lack of sensitivity to polar substituents on nitrogen is in marked contrast to the sizable effects of amine pK_a on the rate constants for uncatalyzed carbinolamine formation in the reaction of weakly basic nucleophiles with *p*-chlorobenzaldehyde,[3] which have been interpreted as indicative of a large positive charge buildup on the nucleophile. This observation suggests that for the amide adducts (as opposed to simple carbinolamines) there is little charge development on the amide, and is consistent with a transition state in which cyclic internal proton transfer to oxygen either directly (**13**) or via one or more water molecules



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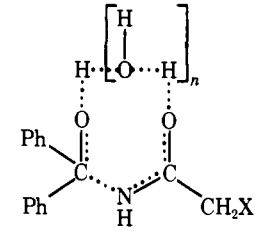

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(**14**) aids in the expulsion of an imidate leaving group.

Experimental Section

Materials. Organic compounds, except for formic and acetic acids, were recrystallized or distilled before use. Reagent-grade inorganic compounds and formic and acetic acids were used without further purification. Water was purified by distillation in a glass apparatus or by passage through a Barnsted Nanopure Water system containing deionizers, an organic removal module, and submicron filter.

Benzophenone imine (**1**) was prepared by the method of Pickard and Tolbert[31] from 0.14 mol of bromobenzene and 0.125 mol of benzonitrile. Substituted imines **2** and **3** were prepared from **1** by transimination. For preparation of **2**, equimolar quantities of cyanoethylamine, **1**, and glacial acetic acid were mixed and the product was recrystallized from hexane, or from ether and then hexane: mp 85–87 °C; NMR (CD_3CN, Me_4Si) δ 2.65 (t), 3.44 (t), 7.02–7.55 (m), relative intensities 1:1:5; IR (KBr) 2250, 1620 cm^{-1}. Further purification of an analytical sample was accomplished by sublimation.

Anal.[32] ($C_{16}H_{14}N_2$) C, H, N.

Cyanomethyl imine **3** was prepared from a 2:1:1 molar ratio of **1**, acetic acid, and aminoacetonitrile hydrochloride in acetonitrile. After refluxing for ~16 h the mixture was filtered to remove the hydrochloride of **1** and the product after solvent evaporation was recrystallized twice from hexane: mp 79–81 °C; NMR (CD_3CN, Me_4Si) δ 4.24 (s), 7.12–7.82 (m), relative intensities 1:5.

Anal.[32] ($C_{15}H_{12}N_2$) C, H, N.

N-Acetylbenzophenone imine **4** was prepared from an equimolar mixture of **1** and acetic anhydride in the absence of solvent: bp 115

°C (0.02 mm) (lit. bp 168–171 °C (1 mm));[10a] NMR (CCl_4, Me_4Si) δ 1.95 (s), 7.60–7.85 (m); IR 1705, 1685, 1630 cm^{-1}.

N-Acylimines **5** and **6** were prepared from equimolar quantities of **1**, triethylamine, and methoxyacetyl chloride or chloroacetyl chloride in toluene. After removal of triethylamine hydrochloride by filtration and evaporation of the solvent the products were purified by dry column chromatography[33] on silica (Brockman activity III, 30 mm), using 20% ether/80% hexane. After chromatography and several recrystallizations from hexane, **6** had mp 63–65 °C (lit. 61–63 °C);[10a] NMR ($CDCl_3$, Me_4Si) δ 4.00 (s), 7.4–7.6 (m). Liquid **5** obtained from dry column chromatography had NMR ($CDCl_3$, Me_4Si) δ 3.24 (s), 3.88 (s), 7.4–7.6 (m).

Kinetics. Reaction rates were measured spectrophotometrically in aqueous solution at ionic strength 1.0 M (KCl) at 25 °C, using a Bausch and Lomb Spectronic 710 spectrophotometer equippped with a thermostated cell compartment, a recorder, and a Caltronics Linear Auto-Expander for recorder scale expansion. The hydrolyses of **1** and **2**, and **3** at pH values below 2.8, were followed at 300 nm, and the hydrolysis of **3** at pH values above 2.8 was followed at 252 nm. Half-times and pseudo-first-order rate constants were determined from semilogarithmic plots of $A_t - A_\infty$ (at 300 nm) or $A_\infty - A_t$ (at 252 nm) against time for 2–4 half-times. Reactions were ordinarily initiated by the addition of 50 or 100 μL of 0.0015–0.003 M acetonitrile solutions of the appropriate imines to 3.0 mL of aqueous buffers to give a final imine concentration of 5×10^{-5} M.

Addition of **4**, **5**, and **6** to aqueous solutions results in an initial rapid absorbance decrease at 260 nm corresponding to imine hydration, followed by a slower absorbance increase due to formation of benzophenone from the carbinolamide. For reactions at low pH pseudo-first-order kinetics of this second phase of the reaction were followed at 260 nm, using a total imine concentration of 5×10^{-5} M. At higher pH values, where this reaction is inconveniently slow, initial rates for the second phase of the reaction of 10^{-4} M imine were measured for approximately 6% of the total reaction at 260 or 280 nm. End points (A_∞) were determined by neutralization and appropriate dilution of a reaction mixture containing 10^{-3} M imine that had been allowed to hydrolyze in 1.0 M HCl. Where necessary, correction was made for reactant absorbance (A_R) by extrapolating the linear portion of plots of absorbance increase vs. time (after the rapid initial absorbance decrease) to time zero. Pseudo-first-order rate constants were determined from the relationship $k_{obsd} = (\Delta A/\Delta t)_{init}/(A_\infty - A_R)$. Values of k_{obsd} determined from initial rate experiments agreed well with those determined in the conventional manner at lower pH values.

Measurement of pK_as. The pK_a value of cyanomethylamine was determined by potentiometric titration at 25 °C of the hydrochloride (0.05 M) with 0.9 M potassium hydroxide in the presence of sufficient potassium chloride to give a total ionic strength of 1.0 M. The pK_a of **2** was determined spectrophotometrically by measurement of the absorption (extrapolated to time zero) at 300 nm of 10^{-4} M **2** in a series of buffer solutions of pH 2.0–6.7. The pK_a of **3** was determined from the pH dependence of the observed rate constant at zero buffer concentration, k^0_{obsd}, at pH 1.5–3.6. A plot of log $[k^0_{obsd}(k_a - k^0_{obsd})]$, where k_a is the observed pH-independent rate constant at low pH, against pH gives a line of slope −1.0 with an x intercept equal to the pK_a.

Product Analyses. Hydrolysis of **2** was shown to give only benzophenone and cyanoethylamine, from the identity of an NMR spectrum of a reaction mixture containing **2** and formic acid buffer, 50% base, in D_2O/CD_3CN, with the combined spectra of authentic benzophenone and cyanoethylamine. Hydrolysis of *N*-acylimines **4**–**6** gives benzophenone, which was identified by thin layer chromatography on silica using 50% ether–hexane as solvent. Hydrolysis of 211 mg of **4** in 15 mL of 50% aqueous acetonitrile containing 1 M hydrochloric acid, followed by extraction of benzophenone with ether and evaporation of the aqueous acid layer, gave 81 mg (0.53 mmol, 100%) of crude $(CH_3CONH_2)_2$·HCl. After purification by sublimation this product had mp 127–130 °C (lit. 131 °C)[34] and equivalent weight (by titration) of 159 (theory 154.5). Hydrolysis of 250 mg of **6** in an aqueous acetonitrile solution containing acetic acid, followed by solvent evaporation, gave a crude residue whose NMR spectrum (in CD_3CN) exhibited as the only nonaromatic peak a sharp singlet at 4.04 ppm that was easily distinguishable from that of chloroacetic acid and remained a single peak when authentic 2-chloroacetamide was added.

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References and Notes

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(2) Rosenberg, S.; Silver, S. M.; Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7986.
(3) Sayer, J. M.; Pinsky, B.; Schonbrunn, A.; Washtien, W. *J. Am. Chem. Soc.* **1974**, *96*, 7998.
(4) Abrams, W. R.; Kallen, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 7777.
(5) Jencks, W. P.; Sayer, J. M. *Faraday Symp. Chem. Soc.* **1975**, *10*, 41.
(6) Sayer, J. M.; Edman, C. *J. Am. Chem. Soc.* **1979**, *101*, 3010.
(7) Wolfenden, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 2763.
(8) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 962.
(9) Koehler, K.; Sandstrom, W.; Cordes, E. H. *J. Am. Chem. Soc.* **1964**, *86*, 2413.
(10) (a) Banfield, J. E.; Brown, G. M.; Davey, F. H.; Davies, W.; Ramsay, T. H. *Aust. J. Sci. Res., Ser. A* **1948**, *1*, 330. (b) Heng Suen, Y.; Horeau, A.; Kagan H. B. *Bull. Soc. Chim. Fr.* **1965**, 1454. (c) Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron* **1967**, *23*, 2869. (d) Drach, B. S.; Dolgushina, I. Yu; Sinitsa, A. D.; Kirsanov, A. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1972**, *42*, 776.
(11) Cyanoacetamide slightly accelerates the hydrolysis of **6** at pH 2.2 and retards it at pH 1.6, presumably as a result of different effects on k_1^0 and k_1^H. The observed effects of this amide at pH 2.2 and 1.6 were used to correct the apparent catalytic constants for cyanoacetic acid at pH 2.30 (52% acid) and 1.73 (80% acid), respectively.
(12) Hine, J.; Craig, Jr., J. C.; Underwood, II, J. G.; Via, F. A. *J. Am. Chem. Soc.* **1970**, *92*, 5194.
(13) Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 3505.
(14) Page, M. I.; Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 8818.
(15) A pK_a of 7.4 is estimated for ionization of the proton on nitrogen of T^+ derived from **1**, as follows. A value of 8.83 is estimated[12,16] for the pK_a of $HOCH_2NH_2CH_3^+$ at 25 °C. Substitution of the two hydrogens on carbon of formaldehyde in this adduct by phenyl groups ($\sigma_I = 0.10$)[17] should decrease the pK_a by 1.68 units, to 7.15, if ρ_I is taken[16] as 8.4. Substitution of a methyl group for hydrogen raises the pK of methylbenzylammonium ion 0.24 units relative to benzylammonium,[18] giving pK_a = 7.4 for T^+. Values of ΔpK_a for substitution of a methyl group in $HOC(Ph)_2NH_2CH_3^+$ by cyanoethyl and cyanomethyl are −2.7 and −5.4, respectively, based on the difference in pK_a values (at 25 °C, ionic strength 1.0) between methylamine[13] and cyanoethyl- or cyanomethylamine giving pK_a values of *4.5* and *1.8* for T^+ intermediates derived from **2** and **3**, respectively.
(16) Fox, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 1436.
(17) Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323.
(18) Carothers, W. H.; Bickford, C. F.; Hurwitz, G. J. *J. Am. Chem. Soc.* **1927**, *49*, 2908.
(19) Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731.
(20) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.
(21) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931.
(22) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.
(23) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154.
(24) Hine, J.; Kokesh, F. C. *J. Am. Chem. Soc.* **1970**, *92*, 4383.
(25) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 1206.
(26) Kluger, R.; Lam, C.-H. *J. Am. Chem. Soc.* **1976**, *98*, 4154. Kluger, R.; Chin, J.; Choy, W.-W. *Ibid.* **1979**, *101*, 6976.
(27) Molday, R. S.; Kallen, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 6739. Fersht, A. R. *Ibid.* **1971**, *93*, 3504.
(28) Cunningham, B. A.; Schmir, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 551. Blackburn, G. M.; Jencks, W. P. *Ibid.* **1968**, *90*, 2638. Chaturvedi, R. K.; Schmir, G. L. *Ibid.* **1966**, *90*, 4413. Barnett, R. E.; Jencks, W. P. *Ibid.* **1969**, *91*, 2358. Okuyama, T.; Sahn, D. J.; Schmir, G. L. *Ibid.* **1973**, *95*, 2345. Hogg, J. L.; Jencks, D. A.; Jencks, W. P. *Ibid.* **1977**, *99*, 4772. Lee, Y-N.; Schmir, G. L. *Ibid.* **1979**, *101*, 3026.
(29) Yates, K.; Stevens, J. B. *Can. J. Chem.* **1965**, *43*, 529.
(30) Fall-off factors of 2.0 and 2.5 are used for transmission of substituent effects through nitrogen and carbon, respectively (Fischer, A.; Happer, D. A. R.; Vaughan, J. *J. Chem. Soc.* **1964**, 4060. Pollet, R.; Vanden Eynde, H. *Bull. Soc. Chim. Belg.* **1968**, *77*, 341. Wells, P. R. "Linear Free Energy Relationships"; Academic Press: New York, 1968; p 39.
(31) Pickard, P. L.; Tolbert, T. L. "Organic Syntheses", Collect. Vol. V; Wiley: New York, 1973; p 520.
(32) By Galbraith Laboratories, Inc., Knoxville, Tenn.
(33) Loev, B., Goodman, M. M., *Chem. Ind. (London)* **1967**, 2026.
(34) Kahovec, K.; Knollmüller, K. *Z. Phys. Chem., Abt. B* **1941**, *51*, 49.