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Reactions of α,α,α-Trifluoroacetophenone with Nucleophiles in 10:1 Water:Acetonitrile Solution

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Abstract: Equilibrium constants for reactions of hydrogen peroxide, hydrogen cyanide, bisulfite ion, *n*-butylamine, 2-methoxyethylamine, hydroxylamine, and hydrazine with α,α,α-trifluoroacetophenone in 10:1 H_2O:CH_3CN solution were determined. Kinetics of the reactions of water, hydroxide ion, cyanide ion, sulfite ion, hydroxylamine, and hydrazine with the same ketone were also studied. The reaction of hydroxylamine shows a change in rate-determining step with increase in concentration of catalyzing acids and allows an unusually complete analysis of the steps of the reaction mechanism. Reaction of hydrazine exhibits general-base catalysis, but no change in rate-determining step could be observed. Rate and equilibrium constants are compared with those for similar reactions of the nucleophiles with aldehydes, and relative reactivities are found to differ for the aldehyde and ketone reactions.

Quite generally, the reactions of nucleophiles with carbonyl compounds proceed to the formation of tetrahedral adducts, which may be final products of reaction or intermediates in overall substitution reactions.[1] The tetrahedral adducts may exist in various ionization states, designated T^0, T^+, T^-, and $T^{\pm}$, as shown in Scheme I.

Most studies of carbonyl substitution reactions and of patterns of reactivities of nucleophiles require some knowledge of the rate and equilibrium constants for the individual steps of Scheme I. Frequently, particularly for substitution reactions, these are inaccessable to direct measurement since the adducts are reactive intermediates. The few constants which have been reported have been of great utility in allowing estimates, through application of various linear free energy relationships,[2] of values for those cases where measurement is not possible.

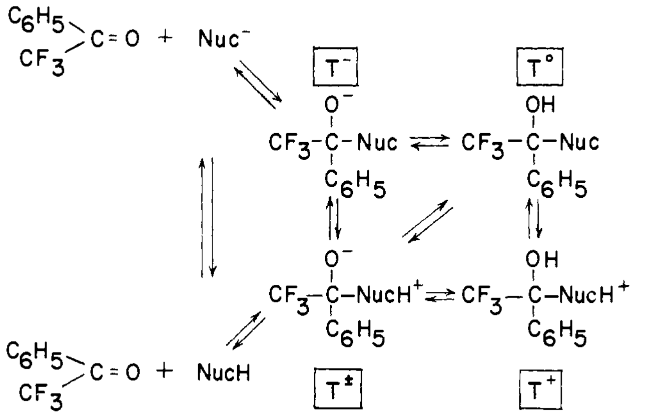
Stewart's reports of his studies of the hydration of α,α,α-trifluoroacetophenones[3] and of the acidities of the hydrates[4] suggested the possibility that reactions of the unsubstituted α,α,α-trifluoroacetophenone with a wide variety of nucleophiles might be amenable to direct study, furnishing an opportunity for greatly expanding the data base of rate and equilibrium constants for such reactions. Although the acidity function approach used for the evaluation of the hydration equilibrium constants is now known to be inaccurate,[5] the hydration constant for α,α,α-trifluoroacetophenone involved a fairly short extrapolation from pure water, and a preliminary measurement of the equilibrium in D_2O solution by ^{19}F NMR gave approximately the same value, 77 for (hydrate)/(ketone), as that reported by Stewart.[3]

The primary difficulty to be overcome is that the extensive hydration of the ketone makes it difficult to observe reactions of other nucleophiles by simply adding the nucleophile to an aqueous solution of ketone. We expected, however, that the hydration reaction would be slower than reactions of most other nucleophiles and that the latter reactions could be studied if the ketone could be mixed rapidly with an aqueous solution of other nucleophile. This expectation has been realized.

Results

Reactions of Water and Hydroxide Ion. Preliminary to the study of other reactions, it was necessary to establish the details of the reactions of water and hydroxide ion with $\alpha,\alpha,\alpha,$-trifluoroacetophenone. Rapid-scanning stop-flow spectrophotometry was used for the study of the hydration reaction in near-neutral water without added buffers or hydroxide ion.

Scheme I



In pure acetonitrile solution, the ketone shows the characteristic conjugated carbonyl absorbance at 256 nm ($\epsilon = 1.3 \times 10^4$ m^{-1} cm^{-1}), with a shoulder at 290 nm. In pure aqueous solution, at equilibrium, one observes only the characteristic aromatic absorbances with three incompletely resolved spikes at 266 nm ($\epsilon = 3.4 \times 10^2$ M^{-1} cm^{-1}), 260 nm ($\epsilon = 4.4 \times 10^2$ m^{-1} cm^{-1}), and 255 nm ($\epsilon = 3.8 \times 10^2$ M^{-1} cm^{-1}) and a shoulder at 250 nm, where the molar absorptivities are calculated on the basis of the total amount of ketone, hydrate + free, in solution.

On mixing one volume of 5.8×10^{-4} M solution of the ketone in acetonitrile with ten volumes of water, the initial spectrum, ca. 5 ms after mixing, is essentially identical with that in pure acetonitrile solution. This spectrum decays with strict first-order kinetics, and with a 2.0-cm observation path, essentially no absorbance is observed at equilibrium. The rate constant for the disappearance of absorbance is 3.2 s^{-1} at 23 °C.

The remainder of the studies were carried out with a single-wavelength stop-flow spectrophotometer at 256 nm and the 10:1 H_2O:CH_3CN mixed solutions.

The dependence of the rate of hydration on hydroxide ion concentration was measured in carbonate–bicarbonate buffers. The pH of the aqueous buffer solutions was measured and it was assumed that the concentration of hydroxide ion was unchanged by the addition of the acetonitrile solution of the ketone. The ionic strength of the aqueous buffers was between 0.01 and 0.02 M, and no dependence of rate on buffer concentration was observed within this range. An excellent linear plot of pseudo-first-order rate constants vs. hydroxide ion concentrations was obtained, giving

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(1) See, for example, Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: New York, 1981; Chapter 8.

(2) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637. Guthrie, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5892. Fastrez, J. *J. Am. Chem. Soc.* **1977**, *99*, 7004.

(3) Stewart, R.; VanDyke, J. D. *Can. J. Chem.* **1970**, *48*, 3961.

(4) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399.

(5) McDonald, R. S.; Teo, K-C.; Stewart, R. *J. Chem. Soc., Perkin Trans. 2*, **1983**, 297.

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Table I. Hydration of α,α,α-Trifluoroacetophenone in 10:1 H_2O:CH_3CN at 23 °C

base catalyst	pK_a of BH^+	rate constant
none		$3.2\ s^{-1}$
OH^- [a]	15.7	$5.0 \times 10^5\ M^{-1}\ s^{-1}$
$H_2NCONHNH_2$	3.8	$25\ M^{-1}\ s^{-1}$
CH_3ONH_2	4.6	$4.5 \times 10^2\ M^{-1}\ s^{-1}$
HPO_4^{2-}	7.2	$21\ M^{-1}\ s^{-1}$
NH_2NH_2	8.3	$6.0 \times 10^2\ M^{-1}\ s^{-1}$
morpholine	8.5	$1.9 \times 10^3\ M^{-1}\ s^{-1}$
Dabco	8.8	$9.4 \times 10^2\ M^{-1}\ s^{-1}$
$MeOCH_2CH_2NH_2$	9.4	$6.6 \times 10^2\ M^{-1}\ s^{-1}$
n-$BuNH_2$	10.6	$1.3 \times 10^3\ M^{-1}\ s^{-1}$

[a] The reaction of hydroxide ion is probably a direct reaction with the ketone, rather than general-base catalysis of the water reaction.

$k_{OH} = 5.0 \times 10^5\ M^{-1}\ s^{-1}$ at 23 °C.

The reaction of the ketone with water shows no acid catalysis; the rate of reaction is the same in pure water, 0.1 M HCl, and 0.1 M acetic acid solutions. The hydration reaction is catalyzed by bases. General base catalysis was studied by the usual techniques of study of rate as a function of base concentration for those bases which show no direct reaction with the ketone. For all of the bases shown in Table I, except *n*-butylamine and hydrazine, the initial absorbances of the reaction solutions are the same as those in the absence of the bases, and the disappearance of absorbance is a strictly first order process. This indicates, as will become apparent in the later results with reactive nucleophiles, that these bases do not react directly with the ketone. Rate constants for general-base catalysis of the water reaction are reported in Table I.

General Characteristics of Reactions of Added Nucleophiles. In aqueous solutions of reactive nucleophiles, two equilibria must be considered:

$$\text{ketone} \rightleftarrows \text{hydrate} \qquad (1)$$

$$K_1 = (\text{hydrate})/(\text{ketone})$$

$$\text{ketone} + \text{HNuc} \rightleftarrows \text{adduct} \qquad (2)$$

$$K_2 = (\text{adduct})/(\text{ketone})(\text{HNuc})$$

where (hydrate) is the sum of the concentrations of the ionization states (T^0 and T^-) of the hydrate, and (adduct) is the sum of the concentrations of the ionization states of the ketone–nucleophile adduct. Both K_1 and K_2 will be pH dependent due to these definitions.

If HNuc is added to an aqueous solution of the ketone in equilibrium with the hydrate, adduct will be formed at the expense of both hydrate and ketone. The kinetics of equilibration need not concern us at present, since these conditions were not used in any of the kinetic studies. The dependence of absorbance of the final equilibrium solution on concentration of HNuc is of interest in connection with the equilibrium constant for cyanohydrin formation. If, at some specific wavelength, the absorbance of the solution in the absence of added nucleophile is A_0, and the absorbance of the solution containing a large excess of HNuc, forcing eq 2 completely to adduct, and the same amount of added ketone, is A_∞, then the absorbance, A, of the solution at intermediate concentrations of HNuc is easily shown to obey eq 3

$$(A_0 - A)/(A - A_\infty) = K_{app}(\text{HNuc}) \qquad (3)$$

where

$$K_{app} = K_2/(1 + K_1) \qquad (4)$$

If ketone is added to an aqueous solution of nucleophile, both reactions 1 and 2 will proceed simultaneously. For the nucleophiles and conditions used here, however, the equilibration of reaction 2 is much faster than that of reaction 1. For all nucleophiles except cyanide ion, we can observe an equilibrium formation of adduct which is much faster than the hydration reaction. Absorbance of the reaction solutions decays in two well-separated pseudo-first-order stages. The absorbances observed at the end of the fast stage vary with concentration of nucelophile as expected for reaction 2 in the absence of reaction 1. The absorbance decays to essentially zero in the slower second stage of reaction. This is the hydration reaction 1 in the presence of a rapid reaction 2, and the rate constant for the second stage is given by[6]

Table II. Reaction of Hydrogen Peroxide with α,α,α-Trifluoroacetophenone in 10:1 H_2O:CH_3CN at 23 °C

pH [a]	$10^3(H_2O_2)$	K_2,[b] M^{-1}
6.86[c]	7.6	23
7.65[c]	7.6	27
7.99[c]	7.6	22
8.30[c]	7.6	26
8.50[c]	7.6	39
8.66[c]	7.6	38
9.17[d]	9.4	89
9.42[d]	9.4	123
9.71[d]	9.3	205
9.95[d]	7.5	191
10.12[d]	9.1	549

[a] Measured pH of the aqueous solution of hydrogen peroxide. [b] Equation 2. [c] Phosphate buffers at ionic strength of 0.01–0.02 M. [d] Carbonate buffers at ionic strength of 0.01–0.02 M.

$$k_\psi = k_h/\{1 + K_2(\text{HNuc})\} \qquad (5)$$

where k_h is the rate constant for the hydration reaction.

Equation 5 serves as a check on the value of K_2 obtained from the initial and final absorbances of the fast stage and may be used to evaluate the general-base catalytic rate constants of the hydration reaction by reactive nucleophiles by solving for k_h and plotting vs. concentration of the nucleophile.

Reaction of Hydrogen Peroxide. With HNuc equal to hydrogen peroxide, reaction 2 reaches equilibrium before the first observation can be made on the stop-flow apparatus. The initial absorbance is lower than that for the same ketone solution mixed with the buffer solution without hydrogen peroxide, and the initial absorbance varies with hydrogen peroxide concentration as expected for reaction 2. The slow further decay of absorbance to zero gives first-order rate constants in accord with eq 5.

The dependence of K_2 on pH is shown in Table II. The increase of K_2 with pH is consistent with a value of 8.8 for the pK of T^0 to give T^- and a value of $K^0 = 25\ M^{-1}$ for the formation of T^0 from ketone and hydrogen peroxide.

Reactions of Sulfite and Bisulfite Ions. With HNuc equal to HSO_3^-, it is possible to observe both stages of reaction discussed above. The final absorbance after the first stage of reaction varies with concentration of HSO_3^- as expected for reaction 2 with $K_2 = 2.3 \times 10^3\ M^{-1}$ over the entire pH range from 4 to 9. The pK_a of the bisulfite adduct (to form dianion) must be greater than 9. Pertinent data are shown in Table III.

The forward rate constant for the fast process is proportional to the concentration of sulfite ion and is independent of concentration of bisulfite ion or buffers. The second-order rate constant for reaction of ketone with sulfite ion is $2.3 \times 10^5\ M^{-1}\ s^{-1}$.

The slower second stage of reaction exhibits rate constants in accord with eq 5. At the fairly low concentrations of sulfite and bisulfite ions used, there is no observable general-base catalysis of the water reaction by these ions.

Reaction of Hydrogen Cyanide. On mixing the acetonitrile solution of ketone with an aqueous solution of hydrogen cyanide buffered at pH of ca. 9, a single first-order decay of absorbance to zero is observed. The pseudo-first-order rate constant, minus that for the hydration reaction in the same buffer without hydrogen cyanide, is proportional to cyanide ion concentration. The second-order rate constant obtained for cyanide reaction is $4.7 \times 10^4\ M^{-1}\ s^{-1}$.

The observed kinetics could represent either general-base catalysis of the hydration reaction by cyanide ion or simultaneous hydration and essentially irreversible formation of cyanide ion

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(6) See, for example: Ritchie, C. D. "Physical Organic Chemistry"; Marcel Dekker: New York, 1975; p 35.

Table III. Reaction of SO_3^{2-} and HSO_3^- with α,α,α-Trifluoroacetophenone in 10:1 H_2O:CH_3CN at 23 °C

buffer	μ,[a] M	10^3-(HSO_3^-)[b]	10^4-(SO_3^{2-})[b]	$10^{-3}K_2$[c]	$10^{-5}k_{SO_3^{2-}}$[d]
HSO_3^-/SO_3^{2-}	0.05	0.12	160	2.4	
HSO_3^-/SO_3^{2-}	0.10	0.22	330	2.3	
$H_2PO_4^-/HPO_4^{2-}$	0.025	0.21	2.1	2.3	
HSO_3^-/SO_3^{2-}	0.005	0.23	18	2.4	
$H_2PO_4^-/HPO_4^{2-}$	0.025	0.28	1.3	2.2	
$H_2PO_4^-/HPO_4^{2-}$	0.025	0.41	4.1	2.6	
HSO_3^-/SO_3^{2-}	0.005	0.52	15	2.0	
$H_2PO_4^-/HPO_4^{2-}$	0.025	0.56	2.6	2.3	
HSO_3^-/SO_3^{2-}	0.005	0.90	18	2.6	
$H_2PO_4^-/HPO_4^{2-}$	0.05	1.0	2.4	1.8	2.4
$H_2PO_4^-/HPO_4^{2-}$	0.05	1.0	4.6	2.3	2.0
$H_2PO_4^-/HPO_4^{2-}$	0.05	1.1	9.4	2.4	
$H_2PO_4^-/HPO_4^{2-}$	0.05	2.3	4.5	2.3	2.6
$H_2PO_4^-/HPO_4^{2-}$	0.05	2.3	6.5	2.1	2.4
$H_2PO_4^-/HPO_4^{2-}$	0.05	2.4	11.1	2.1	1.9
$AcOH/AcO^-$	0.05	2.5	0.14		2.3
$AcOH/AcO^-$	0.05	2.5	0.60		2.4
HSO_3^-/SO_3^{2-}	0.005	2.5	0.55		2.0
$AcOH/AcO^-$	0.05	2.5	1.0		2.5
HSO_3^-/SO_3^{2-}	0.005	2.5	1.1		2.2
$AcOH/AcO^-$	0.05	5.0	0.12		2.8
$AcOH/AcO^-$	0.05	5.0	0.51		2.8
$AcOH/AcO^-$	0.05	5.0	0.97		2.3
HSO_3^-/SO_3^{2-}	0.01	5.0	1.3		1.9

[a] Ionic strength. [b] Concentrations of HSO_3^- and SO_3^{2-} were calculated from the total concentration of sulfite in solution, the measured pH of the aqueous solution of sulfite, and the following "effective pK_a" values for HSO_3^-: 7.20 for μ less than 0.01 M; 7.10 for μ = 0.01–0.05; and 7.00 for μ = 0.10. [c] Equilibrium constant for eq 2. [d] Second-order rate constant for reaction of SO_3^{2-} with the ketone. Obtained by dividing the forward pseudo-first-order rate constant by the concentration of SO_3^{2-}. Units of M^{-1} s^{-1}.

adduct. Since the second-order rate constant is much greater than those reported for general-base catalysis in Table I, it is almost certain that the rate constant is for addition of cyanide ion to ketone. Pertinent data are shown in Table IV.

In order to determine the equilibrium constant for the hydrogen cyanide reaction, conventional spectrophotometry was used with the method described above in connection with eq 3 and 4. In solutions buffered at pH 10.01, ionic strength of 0.5 M, and containing 2.9×10^{-3} M ketone and 1% added acetonitrile, the absorbances at 256, 260, and 266 nm decreased with an increase in cyanide ion concentration as shown in Table IV. A rough Benesi–Hildebrand plot was used to obtain A_∞ values at each wavelength, and equilibrium constants were then calculated from eq 3. The average value of K_{app} obtained is 61 M^{-1} for the reaction of cyanide ion with the ketone to form the T^- species of the cyanohydrin. Since the hydration equilibrium constant for the ketone is 77[3] and the pK_a of the hydrate is 10.0[4], eq 4 gives $K_2 = 9.5 \times 10^3$ M^{-1} for the reaction of ketone with cyanide ion to form T^- cyanohydrin.

In order to be sure that we are indeed observing the formation of T^-, we attempted to observe formation of the T^0 cyanohydrin by adding 9.7×10^{-3} M hydrogen cyanide to a solution of the ketone buffered at pH 6.95. No changes in absorbance were observed. Since we would certainly have observed a change in absorbance if we had half conversion to the cyanohydrin, the K_{app} for reaction of hydrogen cyanide to form T^0 must be much less than 10^2 M^{-1}, and K_2 for the reaction, by eq 4, must be less than ca. 10^4 M^{-1}. Since the pK_a of hydrogen cyanide is 9.1, these observations require that the pK_a of the T^0 form of the cyanohydrin is less than ca. 9. This is consistent with the assignments above.

Reaction of *n*-Butylamine. On mixing an acetonitrile solution of ketone with buffered solutions of *n*-butylamine, the first stage of reaction is over before the first observation can be made on the stop-flow apparatus for all concentrations sufficient to give observable reaction. From the absorbance observed on mixing the same ketone solution with water and with the amine solution, values of K_2 were calculated. All of the experiments with *n*-butylamine were carried out in solutions buffered with *n*-butylammonium ion and with ionic strength of 1.0 M maintained by addition of the required amounts of sodium chloride.

Table IV. Reaction of Cyanide Ion with α,α,α-Trifluoroacetophenone

A. Kinetics in HCO_3^-/CO_3^{2-} Buffers in 10:1 H_2O:CH_3CN at 23 °C

pH	$10^4(CN^-)$[a]	$10^4(HCN)$[a]	k_ψ,[b] s^{-1}	$10^{-4}k_{CN^-}$[c]
8.99	2.00	2.93	9.1	4.5
9.01	4.05	5.80	20.2	5.0
9.24	10.7	9.00	50.2	4.7
9.26	21.9	17.5	102.	4.7

B. Equilibrium at pH 10.01, Carbonate Buffers, μ = 0.50, 99:1 H_2O:CH_3CN, (Total Ketone Concentration = 2.94×10^{-3} M)

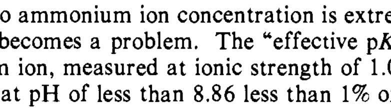
	absorbance at[d] (nm)			K_{app}[e] calcd at (nm)		
$10^3(CN^-)$	256	260	266	256	260	266
0.00	0.922	0.987	0.742			
1.72	0.880	0.935	0.704	94	80	60
3.43	0.876	0.913	0.681	58	65	60
5.15	0.858	0.888	0.658	59	64	60
8.58	0.820	0.832	0.610	72	77	72
7.71	0.841	0.857	0.632	56	64	60
38.5	0.738	0.710	0.510	69	79	63
77.1	0.719	0.682	0.491	55	65	44
∞[f]	0.672	0.623	0.419			

[a] Calculated from the measured pH of the aqueous solution and the total cyanide concentration, using pK_a = 9.14 for HCN. [b] Observed pseudo-first-order rate constant minus that for the hydration reaction at the same pH. [c] Second-order rate constant for reaction of cyanide ion. Units of M^{-1} s^{-1}. [d] In 1.00-cm pathlength cells. [e] $K_{app} = (A_0 - A)/(A - A_\infty)(CN^-)$. [f] From plots of $1/A$ vs. $1/(CN^-)$, extrapolated to $1/(CN^-) = 0$.

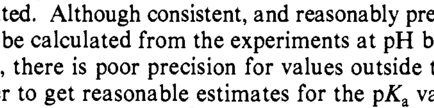
There are serious experimental difficulties at pH greater than 10 and less than 9. At the high pH, the rate of the hydration reaction is great enough that appreciable hydration occurs before the first observation on the stop-flow apparatus. We have attempted to correct for this by "back-extrapolation" of the absorbance to 2 ms before observation. At the low pH, the ratio of amine to ammonium ion concentration is extremely low and buffering becomes a problem. The "effective pK_a" of *n*-butylammonium ion, measured at ionic strength of 1.0 M, is 10.86; therefore, at pH of less than 8.86 less than 1% of the amine is unprotonated. Although consistent, and reasonably precise values of K_2 can be calculated from the experiments at pH between ca. 9 and 10, there is poor precision for values outside this range.

In order to get reasonable estimates for the pK_a values of T^0 to give T^- and of T^+ to give T^0, we have resorted to trial and error fitting of the absorbance and rate data.

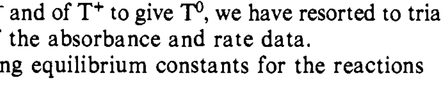
Defining equilibrium constants for the reactions



$$>C{=}O + RNH_2 \overset{K_0}{\rightleftharpoons} HO-C-NHR \qquad (6)$$



$$HO-C-NHR \overset{K_a^0}{\rightleftharpoons} {}^-O-C-NHR + H^+ \qquad (7)$$



$$HO-C-NH_2^+R \overset{K_a^+}{\rightleftharpoons} HO-C-NHR + H^+ \qquad (8)$$

it is simple to show that K_2, in eq 2, is given by

$$K_2 = K_0\{1 + K_a^0/(H^+) + (H^+)/K_a^+\}$$

and that the absorbance of the solution at equilibrium for these reactions is

$$A_i = A^0/\{1 + K_2(RNH_2)\} \qquad (9)$$

where A_i is the (back-extrapolated) initially observed absorbance, and A^0 is the absorbance before reaction, obtained by mixing the

Table V. Reaction of *n*-Butylamine with α,α,α-Trifluoroacetophenone in 10:1 $H_2O:CH_3CN$ at 23 °C, $\mu = 1.0$ M

		A_i		k_ψ[d]	
pH	$10^2(RNH_2)$[a]	obsd[b]	calcd[c]	obsd	calcd[e]
10.84	0.40	0.26	0.46	176	170
10.96	0.92	0.20	0.26	135	128
11.09	2.1	0.15	0.12	108	79
10.68	0.40	0.30	0.50	130	128
10.78	0.92	0.24	0.30	106	100
11.06	2.5	0.18	0.11	74.5	67.2
10.66	1.0	0.26	0.31	79.7	79.7
10.66	2.0	0.23	0.19	53.1	51.7
10.39	0.45	0.46	0.52	73.7	72.0
10.46	1.0	0.36	0.35	61.9	58.2
10.47	2.1	0.22	0.21	43.5	39.2
10.04	0.49	0.56	0.54	30.1	36.6
10.09	2.2	0.26	0.23	21.0	23.6
9.54	0.52	0.42	0.54	16.1	16.1
9.26	0.21	0.59	0.69	11.7	11.4
8.85	0.13	0.72	0.74	5.9	7.0
8.75	0.20	0.68	0.69	6.0	6.7
8.68	1.4	0.35	0.31	13.2	8.7
8.28	0.40	0.55	0.53	6.7	5.7
8.04	0.17	0.66	0.64	5.6	4.4

[a] Calculated from the total concentration of amine, the pH of the aqueous solution, and an "effective pK_a" of 10.86 for *n*-butylammonium ion at 1.0 M ionic strength with NaCl. [b] Initial absorbance back-extrapolated 2 ms. [c] From eq 8 and 9, using values given in the text and $A_0 = 0.85$. [d] The rate constant for the hydration reaction. [e] From eq 5 and 10, using rate and equilibrium constants given in text.

same ketone solution with pure water.

In order to use eq 5 as a further check, we need to know k_h, the rate constant for the hydration reaction in the absence of the amine reaction. This is given by

$$k_h = k_w + k_{OH}(OH^-) + k_{gb}(RNH_2) \tag{10}$$

where k_{gb} is the rate constant for general-base catalysis of the hydration reaction by amine, k_w is the rate constant for reaction of water, and k_{OH} is the rate constant for eaction of hydroxide ion. In separate experiments, we find that $k_w = 3.2$ s^{-1} in 1.0 M NaCl, the same as that in pure water. The value of k_{OH} is 4.4 × 10^5 M^{-1} s^{-1} in 1.0 M NaCl, about 10% lower than that in pure water.

By trial and error, values of $K_0 = 100.$ M^{-1}, $k_{gb} = 1.3 \times 10^3$ M^{-1} s^{-1}, p$K_a^0 = 10.8$, and p$K_a^+ = 8.0$ were found to give reasonable accord with the data. At high pH, greater reliance is placed on the rate data, and at lower pH, more reliance is placed on the absorbance data. Observed and calculated data are shown in Table V.

We estimate that the pK_a values are accurate to ca. ±0.2 units and that K_0 is accurate to ca. ±20%.

Reactions of 2-Methoxyethylamine. As with *n*-butylamine, the first stage of reaction of ketone with methoxyethylamine is too fast to observe. The initial absorbance values give a constant value of $K_2 = 55$ M^{-1} from pH 8.4 to 10.0, and this must be essentially equal to K_0.

The slow stage of reaction gave rate constants in accord with eq 10 and 5 with $k_{gb} = 6.6 \times 10^2$ M^{-1} s^{-1} and the K_2 value obtained from absorbances.

Since K_0 is even smaller than that for *n*-butylamine, no attempt was made to expand the pH range studied to obtain pK_a values of the T^0 and T^+ species.

Reactions of Hydroxylamine. Both stages of reaction may be observed on mixing an acetontrile solution of ketone with the aqueous solutions of hydroxylamine buffered with hydroxylammonium ion. From pH of 4.1 to 6.6, the absorbances at the end of the fast stage of reactions are in accord with eq 9 and $K_2 = 1.5 \times 10^3$ M^{-1}. Since there is no variation of K_2 with pH over this range, K_0 (eq 6) must be equal to K_2. The rate constant for the second, slow stage of reaction varies with hydroxylamine concentration in accord with eq 5 where k_h is just the rate constant for reaction with water, 3.2 s^{-1}.

Table VI. Buffer Catalysis of the Hydroxylamine Reaction in 10:1 $H_2O:CH_3CN$ at 23 °C, $\mu = 0.50$ M

(A) Acetic Acid Buffers, $(CH_3COOH)/(CH_3COO^-) = 0.10$, $(NH_2OH) = 2.0 \times 10^{-3}$ M, $(HONH_3^+) = 1.0 \times 10^{-2}$ M

10^3-(CH_3COOH)	k_ψ obsd[a]	k_ψ calcd[b]	10^3-(CH_3COOH)	k_ψ obsd[a]	k_ψ calcd[b]
0	30.2[c]	27.8	7.5	114	106
1.0	45.6	39.8	8.0	113	111
2.0	55.5[c]	51.2	10.0	127[c]	128
3.0	63.6	62.2	20.0	234[c]	198
4.0	71.1	72.7	30.0	246	249
5.0	82.4	82.9	40.0	263	288
6.0	91.8	92.6			

(B) Phosphate Buffers, $(H_2PO_4^-)/(HPO_4^{2-}) = 1.0$, $(NH_2OH) = 2.0 \times 10^{-3}$ M, $(HONH_3^+) = 1.3 \times 10^{-3}$ M

$10^3(H_2PO_4^-)$	k_ψ obsd[a]	k_ψ calcd[b]	$10^3(H_2PO_4^-)$	k_ψ obsd[a]	k_ψ calcd[b]
0.0	17.6	13.7	8.0	84.0	90.9
1.0	26.0	24.7	10.0	104[c]	107
2.0	35.2	35.2	20.0	170[c]	174
3.0	46.4	45.3	30.0	201	225
4.0	53.9	55.1	40.0	265	264
6.0	73.6	73.6			

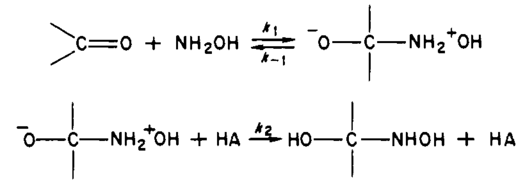
[a] Observed pseudo-first-order rate constant for fast equilibrium. [b] Calculated from eq 13 and $k_\psi = \{1 + 1/K_2(NH_2OH)\}k_\psi^f$, using rate and equilibrium constants given in the text. [c] Average of two determinations.

The forward rate constants for the fast stage of reaction vary with both hydroxylamine and hydroxylammonium ion concentration according to

$$k_\psi^f = (NH_2OH)\{4.5 \times 10^3 + 6.5 \times 10^5(HONH_3^+)\} \tag{11}$$

The dependence on hydroxylammonium ion concentration suggests that the reaction is subject to general-acid catalysis, and this was verified by studies using acetic acid and phosphoric acid buffers. Pertinent data are shown in Table VI.

At low buffer concentrations, the rate constants for the fast reaction increase nearly linearly with buffer concentration, but at higher buffer concentrations, there is a definite levelling off. This behavior is indicative of a change in rate-determining step of the reaction as the concentration of buffer is increased. The simplest mechanism which can account for this is



$$>C{=}O + NH_2OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^-O{-}C{-}NH_2^+OH$$
$${}^-O{-}C{-}NH_2^+OH + HA \xrightarrow{k_2} HO{-}C{-}NHOH + HA$$

(12)

where the second step could involve protonation of $T^\pm$ to form T^+ followed by rapid deprotonation of T^+ to form T^0. There will be a k_2 term for each catalyzing acid in solution. Designating these as k_2^0 for the uncatalyzed, or water-catalyzed term, k_2' for the hydroxylammonium ion term, and k_2'' for the buffer acid term, the pseudo-first-order forward rate constant for the reaction is given by

$$k_\psi^f = k_1(NH_2OH)\frac{\{k_2^0 + k_2'(HONH_3^+) + k_2''(HA)\}}{\{k_{-1} + k_2^0 + k_2'(HONH_3^+) + k_2''(HA)\}} \tag{13}$$

which may be evaluated if values for k_1, k_2^0/k_{-1}, k_2'/k_{-1}, and k_2''/k_{-1} are known. By trial and error, it is found that the data for acetic acid buffers can be fit with $k_1 = 2.2 \times 10^5$ M^{-1} s^{-1} and $k_2''/k_{-1} = 23$ M^{-1}; the values of $k_1k_2^0/k_{-1} = 4.5 \times 10^3$ M^{-1} s^{-1} and $k_1k_2'/k_{-1} = 6.5 \times 10^5$ M^{-2} s^{-1} being known from eq 11. Values of k_ψ^f calculated from eq 13, using these values, are compared with experimental values in Table VI.

Table VII. Buffer Catalysis of Hydrazine Reaction[a] in 10:1 H_2O:CH_3CN at 23 °C

10^3(Dabco)	k_ψ	
	obsd[b]	calcd[c]
0.0	49.7[d]	54.0
0.50	62.2	69.7
1.0	79.9	85.5
2.0	124	117
3.0	149	148

[a] ($DabcoH^+$)/(Dabco) = 2.0; (NH_2NH_2) = 1.0×10^{-3} M; ionic strength of 0.50 M maintained with NaCl. [b] Observed pseudo-first-order rate constant for the fast equilibrium reaction. [c] Calculated from eq 14 with an added term: $(2.1 \times 10^7)(\mathrm{Dabco})(\mathrm{NH_2NH_2})$, and $k_\psi = k_\psi^f\{1 + 1/2.0 \times 10^3(\mathrm{NH_2NH_2})\}$. [d] Average of three determinations.

If the mechanism, eq 12, is correct, the same values for all of the parameters except k_2''/k_{-1} should apply to the reactions catalyzed by the phosphate buffers. A slightly smaller value, $k_2''/k_{-1} = 20$ M^{-1}, with eq 13 gives the values shown in Table VI.

Reaction of Hydrazine. On mixing the acetonitrile solution of ketone with aqueous hydrazine solutions buffered with hydrazinium ion at pH 7.5 to 8.7, both stages of reaction may be observed. From the absorbances at the end of the first stage of reaction, an equilibrium constant, $K_2 = 2.0 \times 10^3$ M^{-1}, for the formation of adduct is found. The value does not vary with pH in the range studied, and must be equal to K_0 for eq 6.

The forward rate constant for the fast stage of reaction varies with hydrazine concentration according to eq 14

$$k_\psi^f = 1.7 \times 10^4(\mathrm{NH_2NH_2}) + 1.9 \times 10^7(\mathrm{NH_2NH_2})^2 \qquad (14)$$

There is no dependence of rate on pH or hydrazinium ion concentration in the ranges studied.

The second-order term in hydrazine suggests that the reaction is general-base catalyzed. This was confirmed by studies using Dabco (1,4-diazabicyclo[2.2.2]octane) buffers. Pertinent data are shown in Table VII. Up to the highest concentration of Dabco which allowed accurate rate measurements, the pseudo-first-order rate constants were linearly dependent on the Dabco concentration. From the slope, $k = 2.1 \times 10^7$ M^{-2} s^{-1} for the coefficient of the (NH_2NH_2)(Dabco) term added to eq 14.

The second, slow stage of reaction gave rate constants consistent with eq 5 and 10 with $k_{gb} = 6 \times 10^2$ M^{-1} s^{-1} for catalysis of the hydration reaction by hydrazine.

Experimental Section

Materials. α,α,α-Trifluoroacetophenone (Fairfield Chemical Co.) was used as received. The UV spectral characteristics in both water and hexane solutions closely matched those reported by Stewart.[3] Solutions of the ketone in acetonitrile exposed to light became brownish after a few days, but when stored in the dark they were stable for several months.

Sources of other materials, and the preparation of standard solutions of sodium sulfite and hydrogen peroxide, were as given in previous reports.[7]

Solutions of hydrazine, prepared by neutralization of $NH_2NH_2 \cdot H_2SO_4$, were handled under a nitrogen blanket and were used in the reaction studies within an hour of preparation.

Apparatus. Conventional spectrophotometry utilized a Cary 210+ UV-Vis spectrophotometer with cell holders and compartment thermostated at 25 °C.

The rapid-scanning stop-flow spectrophotometer described in earlier work[8] was modified in that the drive syringes were a 5.0-mL gas-tight syringe for the aqueous solution and a 0.50-mL gas-tight syringe for the acetonitrile solution of the ketone. The single-wavelength stop-flow apparatus was similarly modified.

Measurements of pH utilized a Corning Model 130 pH meter equipped with glass and saturated calomel electrodes. The meter was standardized within one pH unit of that to be measured.

General Procedures. A master solution, containing 0.294 M ketone in reagent grade acetonitrile, was prepared and stored in the dark. Portions of this solution were diluted to 2.94×10^{-4} M for use in the reaction studies. At the beginning and end of each series of reaction studies, the dilute ketone solution was mixed with pure water in the stop-flow. The initial absorbances of these runs, which are the absorbances before any reaction of ketone, were used in the calculations of equilibrium constants for the reactions being studied.

Table VIII. Summary of Rate and Equilibrium Constants

reaction[a]	log K[b]	log k[b]
$R_2CO + H_2O \rightleftharpoons R_2C(OH)_2$	1.89[c]	0.51[c]
$R_2CO + OH^- \rightleftharpoons R_2C(OH)(O^-)$	5.89[d]	5.70
$R_2C(OH)_2 \rightleftharpoons R_2C(OH)(O^-) + H^+$	−10.00[d]	
$R_2CO + H_2O_2 \rightleftharpoons R_2C(OH)(OOH)$	1.40	
$R_2C(OH)(OOH) \rightleftharpoons R_2C(OH)(OO^-) + H^+$	−8.8	
$R_2CO + HSO_3^- \rightleftharpoons R_2C(OH)(SO_3^-)$	3.36	
$R_2CO + SO_3^{2-} \rightleftharpoons R_2C(O^-)(SO_3^-)$		5.36
$R_2CO + HCN \rightleftharpoons R_2C(OH)(CN)$	(2.88)[e]	
$R_2CO + CN^- \rightleftharpoons R_2C(O^-)(CN)$	3.98	4.67
$R_2CO + BuNH_2 \rightleftharpoons R_2C(OH)(NHBu)$	2.00	
$R_2C(OH)(NHBu) \rightleftharpoons R_2C(O^-)(NHBu) + H^+$	−10.8	
$R_2C(OH)(NH_2^+Bu) \rightleftharpoons R_2C(OH)(NHBu) + H^+$	−8.0	
$R_2CO + MeOCH_2CH_2NH_2 \rightleftharpoons R_2C(OH)(NHCH_2CH_2OMe)$	1.74	
$R_2CO + NH_2OH \rightleftharpoons R_2C(O^-)(NH_2^+OH)$	−3.0[e]	5.34
$R_2C(O^-)(NH_2^+OH) \rightleftharpoons R_2C(OH)(NHOH)$	6.17[e]	6.65[e]
$R_2C(OH)(NHOH) \rightleftharpoons R_2C(O^-)(NHOH) + H^+$	(−10.8)[e]	
$R_2C(OH)(NH_2^+OH) \rightleftharpoons R_2C(O^-)(NH_2^+OH) + H^+$	(−7.5)[e]	
$R_2CO + NH_2NH_2 \rightleftharpoons R_2C(OH)(NHNH_2)$	3.3	
$R_2C(O^-)(NH_2^+NH_2) \rightleftharpoons R_2C(OH)(NHNH_2)$	(4.7)[e]	(5.63)[e]
$R_2C(OH)(NHNH_2) \rightleftharpoons R_2C(O^-)(NHNH_2) + H^+$	(−10.8)[e]	
$R_2C(OH)(NH_2^+NH_2) \rightleftharpoons R_2C(O^-)(NH_2^+NH_2) + H^+$	(−7.5)[e]	

[a] In 10:1 H_2O:CH_3CN at 23 °C. R_2CO is α,α,α-trifluoroacetophenone. [b] Rate and equilibrium constants are for reactions in the direction shown, and units are in molarity and seconds. [c] Unit activity of water. K is from ref 3. [d] From ref 4. [e] Estimated values, see text. Those values in parentheses are considered to be somewhat less reliable estimates than those not in parentheses.

Solutions of the nucleophilic reagents in aqueous solution were prepared and the pH was measured. It is assumed that the pH of the reaction solutions, formed by mixing these solutions 10:1 with the acetonitrile solution of ketone, are the same as those of the aqueous solutions.

The acetonitrile solution of the ketone was loaded into the 0.50-mL driving syringe of the stop-flow apparatus, and the aqueous solution of reactant was loaded into the 5.0-mL driving syringe. A single filling of the drive syringes is sufficient for ca. six kinetic shots. The apparatus is flushed with four fillings of the syringes before each solution is studied.

The output of the photomultiplier was passed to an emitter-follower, and the voltage output was simultaneously recorded on two Nicolet Digital Oscilloscopes. One of the scopes was set at a scan rate, typically 0.1 to 0.5 ms/point, to resolve the fast stage of reaction, and the other at a slower scan rate, typically 2 to 10 ms/point, to observe the slow stage of reaction. Each oscilloscope collects 1024 data points in a scan. Four kinetic "shots" are made and data stored in the four quadrants of the oscilloscope memories. If the four traces on each oscilloscope do not superimpose, the syringes are refilled and the procedure is repeated.

The voltage/time data in a quadrant of memory (1024 points of 12 bit data) are then transferred to a Nova 3/12 computer and stored on hard disk. Voltages are converted to absorbances, and the absorbance/time data are treated by a non-linear least-squares fitting to obtain first-order rate constants and initial and final absorbance values.[9] Finally, a plot of the observed absorbance/time curve is compared with the least-squares curve on a Hewlett-Packard digital plotter interfaced with the computer.

Discussion

The various rate and equilibrium constants obtained are collected in Table VIII, along with some data from other work and some constants which are estimated by procedures to be discussed below.

Hydration Reaction. The equilibrium constant for hydration of trifluoroacetophenone is considerably greater than that of simple ketones, or even of common aldehydes, such as benzaldehyde ($K_h = 8.0 \times 10^{-3}$),[10] but it is comparable to that of reactive ketones,

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such as 1,3-dichloroacetone ($K_h = 10$).[11] It is considerably smaller than that of formaldehyde ($K_h = 1.8 \times 10^3$).[11]

The rate constant for the uncatalyzed hydration reaction, 3.2 s^{-1}, is only slightly less than that for the hydration of formaldehyde,[12] 7.6 s^{-1}. Most notable is the absence of observable acid catalysis for the hydration of trifluoroacetophenone. Acid catalysis is quite prominent for formaldehyde[12] and for substituted benzaldehyde[10] hydrations. McCelland[10] has shown that the Hammett ρ value for the hydrogen ion catalyzed hydration of substituted benzaldehydes is -0.3, while that for the uncatalyzed hydration is $+2.1$. Thus, as the aldehydes become more reactive toward hydration, the contribution of acid catalysis becomes less prominent.

The hydration of trifluoroacetophenone is catalyzed by bases, as is the hydration of formaldehyde[12] and benzaldehydes.[10] There is, however, no obvious Broøsted relationship for the hydration of trifluoroacetophenone catalyzed by the wide range of structural types of bases shown in Table I. Even if one considers similar structural types, such as 2-methoxyethylamine and *n*-butylamine, any Brønsted relationship must have a very small slope. This is in accord with McCelland's observations[10] that Brønsted β values decrease as the reactivities of benzaldehydes toward hydration increase.

In Jencks' terms,[13] both acid and base catalysis decrease in importance as they are less needed. The presence of the strongly electron-withdrawing trifluoromethyl group makes catalysis of the hydration less needed.

From the hydration equilibrium constant and the pK_a of the hydrate,[4] 10.0, of trifluoroacetophenone, the equilibrium constant for the addition of hydroxide ion to the ketone to form T^- is 7.7×10^5 M^{-1}. The rate constant for this reaction is 5.0×10^5 M^{-1} s^{-1}. For reaction of formaldehyde with hydroxide ion, the equilibrium constant to form T^- is 9.0×10^3 M^{-1} (from the hydration constant and the reported[11] $pK_a = 13.3$ for the hydrate), and the rate constant is 3.8×10^6 M^{-1} s^{-1}.[12] In spite of the fact that the ratio of equilibrium constants for hydration and formation of T^- are different for formaldehyde and trifluoroacetophenone (K_{OH}/K_h = 5 and 10^5, respectively), the ratio of rate constants for reaction of hydroxide ion and water are nearly the same (5.0×10^5 and 1.5×10^5, respectively). The rate ratios are smaller than those of ca. 10^7 reported for substituted benzaldehydes, however.

Reaction of Hydrogen Peroxide. Sander and Jencks have reported studies of both the kinetics[14] and equilibria of reactions of hydrogen peroxide with benzaldehydes and have summarized earlier literature on reactions with formaldehyde and acetaldehyde. For *p*-chlorobenzaldehyde, formaldehyde, and acetaldehyde, the equilibrium constants for reaction of H_2O_2 to form the T^0 species are 0.88, 7×10^4, and 48 M^{-1}, respectively, and the ratio $K_{H_2O_2}/K_h$ is 55, 35, and 34 M^{-1}, respectively. For trifluoroacetophenone, the equilibrium constant for formation of T^0 is 25 M^{-1}, and the ratio is 0.32 M^{-1}. If the equilibrium constant for hydration of trifluoroacetophenone is placed on a molar basis by dividing by 55 M, the ratio of equilibrium constants for water and hydrogen peroxide becomes greater than unity, so that, even for trifluoroacetophenone, hydrogen peroxide is more reactive than water.

The pK_a of the T^0 peroxide adduct to give T^-, 8.8, is almost certainly due to the ionization of the hydroperoxy group rather than the hydroxy group since hydroperoxides are generally several p*K* units more acidic than the corresponding alcohols. Since, however, the pK_a of the trifluoroacetophenone hydrate is 10.0, and the peroxy group is expected to be slightly more electron withdrawing than a hydroxy group, the pK_a for ionization of the hydroxy group of the peroxide adduct must not be too much greater than that for the ionization of the peroxy group.

Reactions of Sulfite and Bisulfite Ions. Rate and equilibrium constants for the reactions of isobutyraldehyde[16] and of acetophenone[17] with sulfite and bisulfite ions have been reported by other workers. Most of the general features of reaction noted in those studies are also found in the reaction of trifluoroacetophenone. The reaction rates are first order with respect to sulfite ion concentration, and sulfite ion is much more reactive than is bisulfite ion. For both trifluoroacetophenone and isobutyraldehyde, no dependence of rate on bisulfite ion concentration was found. For acetophenone, the dissociation of the bisulfide adduct was found to exhibit weak general-acid catalysis which, in the addition direction, was interpreted to be specific-acid, general-base catalysis of the addition of bisulfite ion. The catalysis is so weak, however, that it would not have been detected in the present studies.

The equilibrium constant for reaction of bisulfite ion with ketone to form the bisulfite adduct is 2.3×10^3 M^{-1} for trifluoroacetophenone and 5.5 M^{-1} for acetophenone;[17] the rate constants for reactions of sulfite ion are 2.3×10^5 and 77. M^{-1} s^{-1}, respectively. Using $\sigma_I = 0.40$[18] for the CF_3 group and 0.0 for the methyl group, we obtain $\rho_I = 6.6$ for the formation of busulfite adducts and $\rho_I = 8.7$ for the rates of sulfite ion reactions. The corresponding Hammett ρ values for substituted acetophenones are reported[19] to be 1.2 and 1.8, respectively. The larger ρ values for the sulfite ion rates are expected since the dianionic adduct is being formed, while the equilibria are for formation of the monoanionic adduct.

In the present study, it was not possible to observe the ionization of the bisulfite adduct to form the dianionic adduct. The pK_a of the bisulfite adduct cannot be less than 9.0, or we would have detected it. The experimental difficulties of studies much above pH 9.0 arise primarily from the very strong absorbance of sulfite ion in the UV spectrum. Hine[16] has reported a pK_a of 11.7 for the bisulfite adduct of isobutyraldehyde, and Kokesh and Hall[20] have reported a pK_a of 10.7 for the bisulfite adduct of benzaldehyde. These values are surprising in that they are considerably lower than the pK_a values of the corresponding hydrates, 13.8 for isobutyraldehyde[21] and 12.6 for benzaldehyde.[10] One certainly expects the electron-withdrawing ability of the SO_3^- group to be less than that of the hydroxyl group.[18] The detailed data[16] reported by Hine show considerable scatter at high pH, and small differences in very large absorbances of solutions are involved. Although detailed data are not reported by Kokesh and Hall,[20] the same problem of very high absorbances must have been encountered since measurements were made at 250 nm. In view of these considerations, and of the possibility of base-catalyzed side reactions of the aldehydes studied, these pK_a values of the bisulfite adducts should be regarded with some skepticism.

For trifluoroacetophenone reactions, the equilibrium constant for bisulfite addition is larger than that for hydration by a factor of 30 M^{-1}. For isobutyraldehyde reactions, the corresponding factor is 7.8×10^4 M^{-1}. As with the equilibrium addition of hydrogen peroxide discussed above, the addition of bisulfite, relative to water, is much less favorable for ketone than for aldehydes.

Reaction of Hydrogen Cyanide. If the pK_a of the cyanohydrin of trifluoroacetophenone were known, it could be used with the measured equilibrium constant for addition of cyanide ion to form the T^- cyanohydrin, and the known pK_a of hydrogen cyanide, to obtain the equilibrium constant for addition of hydrogen cyanide to form the T^0 cyanohydrin. From the experimental observations, only an upper limit of ca. 9 can be set on the pK_a of the cyanohydrin.

The pK_a of the cyanohydrin of benzaldehyde has been reported[22] as 10.7. This is 1.9 units lower than the reported[23] pK_a of the hydrate of benzaldehyde. Since the pK_a of the hydrate of tri-

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fluoroacetophenone is 10.0[4], the pK_a of the cyanohydrin is then estimated as 8.1.

Alternatively, the ρ value for the ionization of alcohols,[24] $\rho_I = 8.4$, the σ values for OH and CN, $\sigma_I = 0.24$ and 0.57, respectively,[18] and the "statistically corrected" pK_a of the hydrate of trifluoroacetophenone, 10.3, lead to an estimate of $pK_a = 7.5$ for the cyanohydrin of trifluoroacetophenone.

When the order-of-magnitude estimate of 8.0 for the pK_a of the cyanohydrin is used, the approximate average of the above two estimates, the equilibrium constant for the addition of hydrogen cyanide to trifluoroacetophenone to form the T^0 cyanohydrin is 7.5×10^2 M^{-1}.

The equilibrium constant for the addition of hydrogen cyanide to benzaldehyde to form T^0 cyanohydrin is[22] 2.3×10^2 M^{-1}. The ratio K_{HCN}/K_{H_2O} is 2.9×10^4 M^{-1} for benzaldehyde and ca. 10 M^{-1} for trifluoroacetophenone.

The rate constant for reaction of cyanide ion with trifluoroacetophenone, 4.7×10^4 M^{-1} s^{-1}, is much greater than that for reaction with benzaldehyde,[22] 68 M^{-1} s^{-1}. The ratio of rate constants, 6.9×10^2, may be compared with the ratio of equilibrium constants for the formation of T^- cyanohydrin for trifluoroacetophenone and benzaldehyde, which is 1.7×10^3.

Reaction of *n*-Butylamine. The equilibrium constant for the reaction of *n*-butylamine with trifluoroacetophenone to form the T^0 carbinolamine is 100 M^{-1}, the pK_a of the T^0 species, to form T^-, is ca. 10.8, and the pK_a of the T^+ species (Scheme I), to form T^0, is ca. 8.0.

As with the addition of other neutral reagents, relative to water, the addition of *n*-butylamine to trifluoroacetophenone is less favorable than might have been expected from comparable reactions with aldehydes. For aldehydes, the ratio of equilibrium constants, K_{RNH_2}/K_{H_2O}, is approximately 40 to 100 M^{-1} for most aldehydes and amines,[15,25] and 1000 M^{-1} for methylamine with formaldehyde,[15] while it is 1.4 M^{-1} for trifluoroacetophenone.

The pK_a of the T^0 carbinolamine is 0.5 units greater than that of the statistically corrected pK_a of the hydrate as expected from a less positive σ_I value of RNH (0.13[18]) than of OH (0.24[18]). The pK_a of the T^+ species is ca. 3 units lower than that of the *n*-butylammonium ion. One might have expected an even larger difference since the pK_a of trifluoroacetophenone hydrate is ca. 6 units lower than the pK_a's of simple alcohols. The hydroxy, trifluoromethyl benzyl group is obviously strongly electron withdrawing.

Reaction of 2-Methoxyethylamine. The equilibrium constant for the reaction of 2-methoxyethylamine to form the T^0 carbinolamine is only slightly lower than that for the corresponding reaction of *n*-butylamine. The insenstivity of these equilbrium constants to amine structure has been noted in reactions with aldehydes.[15]

Reaction of Hydroxylamine. The present results are in general accord with the detailed mechanism put forward by Sayer and Jencks[24,26] for the formation of carbinolamines from reactions of hydrazine and hydroxylamine derivatives with substituted benzaldehydes. With reference to Scheme I, the mechanism involves formation of $T^\pm$ followed by a proton transfer from any general acid to form T^+ and a very rapid second proton transfer to form T^0. There is also an observable contribution to the kinetics from a step involving direct conversion of $T^\pm$ to T^0, which these workers attributed to a water-mediated isomerization. In addition, there is some evidence for a concerted, general-acid-catalyzed conversion of reactants to T^+, which makes a small contribution to the observed kinetics. Our experiments do not give any detectable contribution from this latter pathway, but we have not searched exhaustively for it.

In the cases studied by Sayer and Jencks, the dehydration of carbinolamine became rate determining at high buffer concentrations and at high pH, so that k_1 of mechanism 12 could not be observed. In the present case, the dehydration reaction does not occur, at least in the time ranges studied, and we have a fairly direct value for $k_1 = 2.2 \times 10^5$ M^{-1} s^{-1}. Since the ratio k_2''/k_{-1} is essentially the same for acetic acid and for $H_2PO_4^-$, k_2'' must be a diffusion-controlled rate constant of ca. 5×10^9 M^{-1} s^{-1}, and from the value of the ratio, 20–23 M^{-1}, $k_{-1} = 2.2 \times 10^8$ s^{-1}. From k_1 and k_{-1}, the value of K_1, the equilibrium constant for formation of $T^\pm$ from reactants, is 1.0×10^{-3} M^{-1}. Sayer and Jencks had to resort to the use of linear free energy relationships to obtain a value of K_1 for their systems. Our value is much more direct, and it depends only on the assignment of a value to k_2''.

The observed kinetic term in hydroxylammonium ions concentration, eq 11, is due, according to the mechanism being discussed, to rapid equilibrium formation of $T^\pm$ and protonation by hydroxylammonium ion to form T^+, with observed rate-constant, 6.5×10^5 M^{-2} s^{-1}, equal to K_1k_2'. From the above value of K_1, we find $k_2' = 6.5 \times 10^8$ M^{-1} s^{-1}, which is a quite reasonable value for a thermodynamically favorable proton transfer from an ammonium ion to an oxide oxygen.

The uncatalyzed, or water catalyzed, rate constant is 4.5×10^3 M^{-1} s^{-1}. This term could arise from rapid equilibrium formation of $T^\pm$ followed either by a proton transfer from water to form T^+ or by an intramolecular proton shift, possibly through water,[24,26] to form T^0 in a single step. The latter appears more reasonable on the basis of the following arguments.

Since acetic acid and $H_2PO_4^-$ protonate $T^\pm$ at the same rate, both of these must be thermodynamically favorable reactions, and the pK_a of T^+ to form $T^\pm$ must, therefore, be greater than the pK_a of $H_2PO_4^-$, ca. 7. The pK_a of T^0 to form T^- must not be very different from that for the carbinolamine formed from *n*-butylamine, 10.8. Protonation of the nitrogen of T^0 to form T^+ must increase the acidity of the carbinol group by at least 2 p*K* units. Thus, the pK_a of T^+ to form $T^\pm$ must be in the range of 7 to 8.8. The rate constant for a proton transfer from water to $T^\pm$ is, therefore, thermodynamically unfavorable by a factor of more than 10^5, and it cannot be greater than ca. 10^5 s^{-1}. Since K_1 is 1.0×10^{-3} M^{-1}, 10^2 M^{-1} s^{-1} is the largest possible value for an observed rate constant for the mechanism involving rapid equilibrium formation of $T^\pm$ followed by proton transfer from water to form T^+. This is more than an order of magnitude less than the observed value.

Assuming that the mechanism for the uncatalyzed reaction is formation of $T^\pm$ followed by isomerization to T^0, the rate constant for the isomerization step is 4.5×10^6 s^{-1}. This is precisely in the range of 10^6 to 10^7 s^{-1} estimated by Jencks[24] for the isomerizations of the benzaldehyde carbinolamines. These rate constants are slightly lower than those of 10^7–10^8 s^{-1} measured by Maas[27] for 2-ammonioethylthiolates and estimated by Sayer[26] for several $T^\pm$ carbinolamines.

The equilibrium constant for the conversion of T^0 to $T^\pm$ can be obtained for the present system from the other constants discussed above. From $K_1 = 1.0 \times 10^{-3}$ M^{-1}, and the equilibrium constant for formation of T^0 from reactants, 1.5×10^3 M^{-1}, the value of K_z is 6.7×10^{-7}. Jencks[28] has estimated a value of 10^{-6} for the equilibrium constant for conversion of T^0 to $T^\pm$ for the carbinolamine from hydroxylamine and *p*-chlorobenzaldehyde. The similarity of the values for the two different systems is expected, since this equilibrium constant should not be very sensitive to polar effects of the groups originally attached to the carbonyl group.[24]

Reaction of Hydrazine. General-base catalysis of carbinolamine formation has been previously observed in the reaction of piperazine with pyridine-4-carboxaldehyde.[29] The mechanism proposed is similar to that discussed above, except that the rate-determining proton transfer is from $T^\pm$ to the base to form T^-.

In the reaction of hydrazine with trifluoroacetophenone, the rate constants for catalysis by hydrazine and by Dabco, 1.9×10^7

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and 2.1 × 10^7 M^{-2} s^{-1}, respectively, are the same within experimental error. This is consistent with the expectation from the proposed mechanism where the proton transfer steps are thermodynamically favorable diffusion-controlled reactions. Estimating the diffusion-controlled rate constant for nitrogen-to-nitrogen proton transfer[30] as 5.0 × 10^8 M^{-1} s^{-1}, the equilibrium constant for formation of $T^{\pm}$ from reactants must be 4.0 × 10^{-2} M^{-1}. Since the overall equilibrium constant for formation of T^0 from reactants is 2.0 × 10^3 M^{-1}, the equilbrium constant for isomerization of T^0 to $T^{\pm}$ is 2.0 × 10^{-5}. This is a factor of 30 larger than the corresponding value for the carbinolamine of hydroxylamine discussed above. Since the pK_a of the hydrazinium ion is ca. 2 units greater than that of the hydroxylammonium ion, we might have expected a factor of 100 difference for the isomerization constants of the corresponding carbinolamines.

The uncatalyzed reaction of hydrazine with trifluoroacetophenone has a rate constant of 1.7 × 10^4 M^{-1} s^{-1}. With the assumption that this represents a rapid equilibrium formation of $T^{\pm}$, followed by isomerization to T^0, the rate constant for the isomerization reaction is 4.3 × 10^5 s^{-1}. This value is a factor of 10 lower than that for the corresponding isomerization of the hydroxylamine carbinolamine.

We can attempt to estimate equilibrium constants for the various interconversions of T species in Scheme I. We define the following equilibrium constants.

$$K_z = (T^{\pm})/(T^0) \qquad (15)$$

$$K_+^{\pm} = (T^{\pm})(H^+)/(T^+) \qquad (16)$$

$$K_{\pm}^- = (T^-)(H^+)/(T^{\pm}) \qquad (17)$$

$$K_+^0 = (T^0)(H^+)/(T^+) \qquad (18)$$

$$K_0^- = (T^-)(H^+)/(T^0) \qquad (19)$$

from which it follows that

$$K_z = K_+^{\pm}/K_+^0 = K_0^-/K_{\pm}^- \qquad (20)$$

Since the σ_I values of alkylamino and hydrazino groups are not much different,[31] the value for K_0^- is expected to be nearly the same for the carbinolamines formed from *n*-butylamine, hydrazine, and hydroxylamine. For *n*-butylamine, the experimental value for log K_0^- is ca. −10.8. For the hydrazine carbinolamine, log K_z = −4.7, and from eq 20, log $K_{\pm}^-$ is then −6.1. Similarly, for the hydroxylamine carbinolamine, log $K_{\pm}^-$ = −4.6.

In order to estimate the other equilibrium constants, we need to know the appropriate value of ρ_I. Jencks[24] uses a value of 8.4, but this seems too high for several reasons. First, the pK_a of the hydrate of trifluoroacetophenone, 10.0, is only 2.6 units lower than that of benzaldehyde hydrate, 12.6.[23] From σ_I = 0.40 for the CF_3 group,[18] ρ_I = 2.6/0.40 = 6.5. Second, as mentioned in the discussion of the reaction of hydrogen cyanide, the difference in pK_a's of benzaldehyde hydrate and cyanohydrin is 1.9 units. Correcting this by +0.3 units for symmetry of the hydrate, and dividing by the difference in the σ values of OH and CN (0.33), we find ρ_I = 6.7. We can make another check of this ρ value from the pK_a of trifluoroethanol, 12.4, the pK_a of trifluoroacetophenone hydrate, 10.0 + 0.3 for symmetry, and the σ_I value for the phenyl (0.12) and hydroxyl (0.24) groups,[18] which lead to a ρ value of 5.8.

With use of ρ_I = 6.5 and a difference in σ_I values of 0.5[31] for the NHR and NH_2^+R groups, log $K_+^{\pm}$ is expected to be 3.3 units greater than log K_0^-. Therefore, log $K_+^{\pm}$ = −7.5 for the species derived from both hydroxylamine and hydrazine. This value is within the range which we set on kinetic grounds in the discussion of the hydroxylamine reaction.

Finally, from eq 20, we find log K_+^0 = −2.8 for the hydrazine adduct and −1.3 for the hydroxylamine adduct.

Table IX. Relative Reactivities of Nucleophiles

(A) Equilibrium Reactivities

	log (K_{HNuc}/K_{H_2O}), M^{-1}	
HNuc	trifluoro-acetophenone	aldehydes[a]
HSO_3^-	1.47	5.86
NH_2NH_2	1.39	2.65
NH_2OH	1.28	3.08
HCN	0.99	4.28
n-$BuNH_2$	0.11	1.49[b]
HOOH	−0.49	1.20

(B) Kinetic Reactivities

	log (k_{Nuc}/k_{OH^-})		
Nuc	trifluoro-acetophenone	formaldehyde	*p*-ClPhCHO
H_2O	−5.19	−5.70[c]	−6.97[d]
CN^-	−1.03	−1.04[e]	−1.38[f]
SO_3^{2-}	−0.34	0.4[g]	1.0[h]
NH_2OH	−0.36		

[a] Derived from $\gamma_{HNuc} - \gamma_{H_2O}$ + 1.74. Data from ref 15. [b] For *n*-propylamine. [c] From ref 12. [d] From ref 10. [e] From ref 32. [f] From ref 22. [g] Data approximated in ref 16. [h] From data for benzaldehyde in ref 16, and correction for the *p*-chloro group as found for reactions of sulfite ion with substituted acetophenones in ref 19.

For the $T^{\pm}$ species formed in the hydroxylamine reaction, a proton transfer from acetic acid, hydroxylammonium ion, or $H_2PO_4^-$, to $T^{\pm}$ to form T^+ is a thermodynamically favorable reaction. So, also, is a proton transfer from $T^{\pm}$ to HPO^{2-}, but not to acetate or hydroxylamine, to form T^-. This furnishes a fairly satisfying rationalization of the observed acid catalysis of the hydroxylamine reaction.

In the case of the hydrazine reaction, the proton transfer from $T^{\pm}$ to hydrazine or to Dabco, to form T^-, is highly favorable. The transfer to $T^{\pm}$ by $DabcoH^+$ is unfavorable by ca. 1.3 p*K* units and by the hydrazinium ion is nearly balanced. Thus, the observed base catalysis of the hydrazine reaction is within reason, although we might have expected that acid catalysis could have been observed since proton transfers to oxygen are usually slightly faster than those to nitrogen,[30] all other factors being equal. A slight increase in the value of $K_+^{\pm}$, however, would completely rationalize the observed catalysis.

Kinetic and Equilibrium Reactivities of Nucleophiles. In Table IX are listed data pertinent to the relative reactivities of nucleophiles with trifluoroacetophenone and with several aldehydes.

In the equilibria, relative to water, all nucleophiles are found to be less reactive with trifluoroacetophenone than with aldehydes. Bisulfite and hydrogen cyanide are particularly unreactive toward trifluoroacetophenone. Sander and Jencks[15] noted that amine nucleophiles, relative to others, were more reactive toward formaldehyde than toward the aromatic aldehydes on which the γ scale was based. Steric effects were suggested as a partial rationalization. The data for trifluoroacetophenone reactions do not appear to be so easily rationalized. Although the low relative reactivity of bisulfite might be ascribed to a steric effect, it is difficult to understand the low reactivity of hydrogen cyanide on this basis.

Whatever the cause of the low equilibrium reactivity of hydrogen cyanide, the rate of reaction of cyanide ion, relative to hydroxide ion, is nearly the same for trifluoroacetophenone as for aldehydes. The rate of reaction of bisulfite ion, relative to hydroxide ion, is lower for trifluoroacetophenone than for aldehydes, but only by a factor of ca. 10, as opposed to the factor of ca. 10^4 for the equilibria.

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Registry No. HOH, 7722-84-1; HCN, 74-90-8; HSO_3^-, 15181-46-1; *n*-$BuNH_2$, 109-73-9; NH_2OH, 7803-49-8; NH_2NH_2, 302-01-2; CN^-, 57-12-5; SO_3^{2-}, 14265-45-3; α,α,α-trifluoroacetophenone, 434-45-7; 2-methoxyethylamine, 109-85-3.

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