

- acidic cation-exchange resin Amberlite 15 ($-\text{SO}_3\text{H}^+$). The obtained solution is titrated by a standard 0.1 N NaOH solution.
- (30) J. C. Trebellas, J. R. Olechowski, H. B. Jonassen, and D. W. Moore, *J. Organomet. Chem.*, **9**, 153 (1967).
 - (31) R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, **93**, 2397 (1971).
 - (32) L. M. Haines, *Inorg. Chem.*, **10**, 1685 (1971).
 - (33) An analogous complex containing both ethylene and dioxygen coordinated on the same metal has been isolated in the case of Iridium— $\text{IrCl}(\text{PPh}_3)_2\text{O}_2(\text{C}_2\text{H}_4)\text{C}_2\text{H}_4$ —H. Van Gaal, H. G. A. H. Cuppers, and A. Ven der Ent, *J. Chem. Soc. D*, 1694 (1970).
 - (34) G. Read et al.⁹ have also suggested the transient formation of a five-membered peroxometalocycle in the cooxygenation of 1-octene and phosphine by $\text{RhCl}(\text{PPh}_3)_3$. However, they supposed that decomposition of [C] would give a dioxetan species and the reduced complex. This dioxetan would be the source of the formation of 2-octanone, heptanal, and phosphine oxide. It seems more likely that decomposition of [C] gives rise to the formation of the oxo species [D], as it is outlined in the text.
 - (35) R. Sheldon, *J. Organomet. Chem.*, **94**, 115 (1975).
 - (36) H. Mimoun, I. Serge de Roch, and L. Sajus, *Tetrahedron*, **26**, 37 (1970).
 - (37) J. E. Bäckwall, B. Åkermark, and S. O. Ljung Green, *J. Chem. Soc., Chem. Commun.*, 264 (1977).
 - (38) W. E. Newton, D. C. Bravard, and J. W. McDonald, *Inorg. Nucl. Chem. Lett.*, **11**, 553 (1975).
 - (39) M. Fremi, D. Giusto, and P. Romiti, *Gazz. Chim. Ital.*, **99**, 641 (1969).
 - (40) A referee suggests that strong acids can react with group 8 metal dioxygen complexes such as [B] to give hydrogen peroxide (S. Muto, H. Ogata, and Y. Kamiya, *Chem. Lett.*, **8**, 809 (1975)). Such a reaction might be the pathway for generating rhodium hydroxy species such as [E]. Such an alternative cannot be excluded, although we have found incidentally that addition of small amounts of 85% H_2O_2 inhibits the catalytic activity under the conditions depicted in Figure 1 and in the presence of excess DMP.
 - (41) I. S. Kolomnikov, Y. D. Koreshkov, I. S. Lobeeva, and M. E. Volpin, *J. Chem. Soc. D*, 1432 (1970).
 - (42) K. B. Sharpless, A. Y. Teranishi, and J. E. Bäckwall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).
 - (43) A. O. Chong, K. Oshima, and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 3420 (1977).
 - (44) E. O. Fisher, and S. Riedmüller, *Chem. Ber.*, **107**, 915 (1974).
 - (45) R. R. Schrock, *J. Am. Chem. Soc.*, **98**, 5399 (1976).
 - (46) A. Van der Ent and A. L. Onderdelinden, *Inorg. Synt.*, **14**, 93 (1973).
 - (47) F. Igersheim and H. Mimoun, *J. Chem. Soc., Chem. Commun.*, 559 (1978).

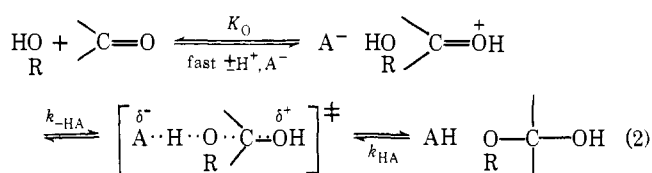
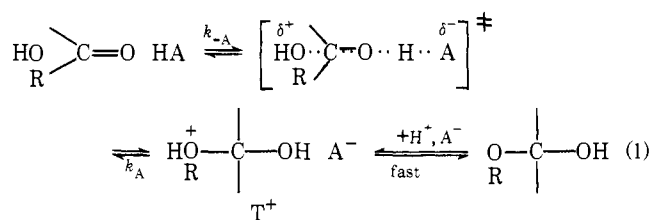
Mechanisms of General Acid and Base Catalysis of the Reactions of Water and Alcohols with Formaldehyde¹

Lance H. Funderburk,*² Lois Aldwin, and William P. Jencks*

Contribution No. 1208 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. Received February 3, 1978

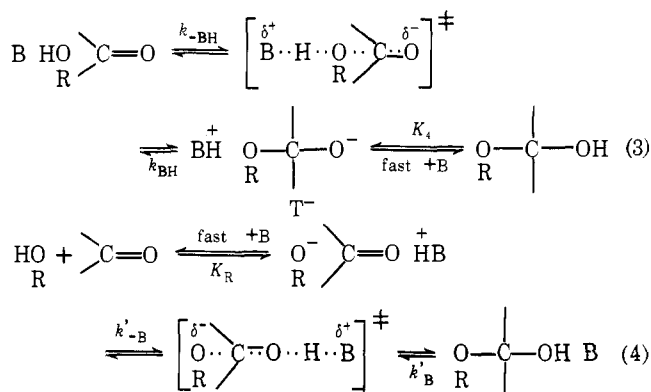
Abstract: The observed general base catalysis of the cleavage and formation of formaldehyde hydrate and hemiacetals proceeds through a class n mechanism involving proton transfer to or from the leaving oxygen atom. This conclusion is based on (1) structure-reactivity relationships with $p_{xy'} = \partial\beta/\partial pK_{1g} = \partial\beta_{1g}/\partial pK_{BH^+} = 0.09$ and $p_{y'} = \partial\beta_{1g}/\partial pK_{1g} = -0.20$ that are expected for this mechanism and are similar to the behavior observed previously for kinetically unambiguous class n catalysis, (2) a requirement for rate constants larger than the diffusion-controlled limit for the acid-catalyzed attack of ethoxide ion on formaldehyde, according to the alternative class e mechanism, and (3) the observation of both rate increases and rate decreases with electron-donating substituents in the leaving alcohol, depending on the pK of the catalyst and leaving group. The structure-reactivity relationships and the rate constants that would be required for a stepwise mechanism provide evidence that proton transfer and C-O cleavage are concerted. The observed general acid catalysis of these reactions proceeds through a class e mechanism with proton transfer to or from the formaldehyde oxygen atom. This conclusion is based on (1) structure-reactivity relationships including a value of $p_{xy} = \partial\alpha/\partial pK_{1g} = 0.022$ that is similar to the value of $p_{xy} = 0.026$ for the general-acid-catalyzed addition of thiol anions to acetaldehyde, (2) comparison of absolute rate constants and α with those for acetal hydrolysis, a model for a class n reaction, and (3) a requirement for rate constants larger than the diffusion-controlled limit for the base-catalyzed hydration of protonated formaldehyde according to the alternative class n mechanism. The values of α , the structure-reactivity relationships, and the rate constants that would be required for a stepwise mechanism show that the mechanism involves a larger component of proton transfer in the transition state compared with the reactions of stronger nucleophiles and continues a trend toward a fully concerted reaction mechanism as the basicity of the attacking nucleophile is decreased. The properties of the transition states of the acid- and base-catalyzed reactions are described in terms of reaction coordinate diagrams that are defined by the observed structure-reactivity relationships.

The observed general acid catalysis of the addition of water to the carbonyl group could occur through either of the kinetically equivalent mechanisms shown in eq 1 and 2 ($R =$



H).³⁻⁵ Equation 1 describes a class e mechanism,⁶ in which the catalyst, HA, acts as a general acid to donate a proton to the oxygen atom of the electrophilic carbonyl group in the forward direction and A^- removes it from the conjugate acid of the addition compound in the reverse direction. Equation 2 describes a class n mechanism in which A^- removes a proton from the oxygen atom of the nucleophilic reagent as it attacks the protonated carbonyl group in the forward direction and HA adds a proton to this oxygen atom as it is expelled in the reverse direction. Thus the observed kinetic general acid catalysis corresponds to true general acid catalysis in the addition direction and to general base catalysis-specific acid catalysis in the reverse direction for a class e mechanism (eq 1); the opposite assignments hold for a class n mechanism. Similarly, the observed kinetic general base catalysis of carbonyl group hydration could occur through either the class n mechanism of eq 3 or the class e mechanism of eq 4.

There is still no general agreement as to which of these mechanisms is correct,⁷ although the fact that the hydrolysis



of ordinary aliphatic acetals does not show general acid catalysis ($\alpha = 1.0$) provides evidence favoring the mechanism of eq 1 over that of eq 2, because acetal hydrolysis is a model for the mechanism of eq 2 from right to left, and the absence of general acid catalysis for the addition of most other strongly basic nucleophiles provides an argument against the mechanism of eq 4.⁵ The reactions could also proceed through cyclic mechanisms involving one or several solvent molecules.⁸ Evidence consistent with such a mechanism has been obtained from the dependence of the reaction rate upon the concentration of water in solutions of low water content, which suggests that several solvent molecules are involved in the transition state, from thermodynamic activation parameters, and from solvent deuterium isotope effects.⁹ However, calculations based on a simplified potential energy surface for single processes with no activation energy, and on isotope effects, suggest that the primary process in general acid catalysis is similar to that shown in eq 1 with only a secondary role for additional solvent molecules, rather than a fully concerted, synchronous, cyclic mechanism.¹⁰ A primary role of proton transfer to or from the buffer base or acid with solvation of the transition state by other molecules is further supported by (1) the absence of a large advantage for catalysis by molecules, such as phosphate, that can transfer protons to and from different atoms simultaneously in a cyclic, bifunctional catalytic mechanism,¹¹ (2) the identical catalytic activity of secondary and tertiary amines^{9e} and the closely similar activities of pyridinium ion and pyridine compared with carboxylic acids and anions of comparable pK ¹² (the nitrogen atom of the pyridinium ion does not have lone pair electrons and tertiary amines do not have an acidic proton to fit into a cyclic transition state), and (3) the fact that the Brønsted α and β values are considerably greater than zero. Positive Brønsted coefficients require that there be net proton donation and abstraction, respectively, by the added molecule of catalyst in the transition state and that the ability of a given acid or base catalyst to bring about this net proton donation or abstraction determines its effectiveness as a catalyst. Thus, there is no evidence for a cyclic transition state in which the catalyst is involved in a synchronous donation and acceptance of protons. The role of additional water molecules is best ascribed to solvation of the transition state and, possibly, to providing bridging molecules for proton transfer and hydrogen bonding. If the reaction does not proceed through a cyclic, synchronous mechanism, the problem then remains of distinguishing between the mechanisms of eq 1 and 2 for general acid catalysis and those of eq 3 and 4 for general base catalysis.

Water is an unsatisfactory reagent to examine with a view to determining reaction mechanisms because it is not possible to vary its concentration or its chemical reactivity as a catalyst, nucleophile, or leaving group, without also changing the properties of the solvent. Accordingly, we have examined the cleavage of a series of formaldehyde hemiacetals (eq 1–4, R = Et, Me, CH₃OEt, ClEt, Cl₂Et, F₃Et) catalyzed by a series

of buffer acids and bases of varying pK , with the goal of utilizing changes in structure–reactivity relationships with changing structure of the reactants and catalysts (1) to diagnose the pathways and (2) to characterize the transition states of the acid- and base-catalyzed reactions. The formation and cleavage of hemiacetals is very similar to the analogous reactions involving water with respect to absolute rate, catalysis, and the dependence of the rate on ROH concentration in nonhydroxylic solvents.^{13–16}

Experimental Section

Materials. Absolute ethanol, methanol, formaldehyde (37% solution stabilized with 12–15% methanol), acetic acid, and inorganic salts were used without further purification. Chloroacetic acid, cyanoacetic acid, 3-chloropropionic acid, thiosemicarbazide, semicarbazide hydrochloride, and hydrazine monohydrochloride were recrystallized before use. Methoxyacetic acid, 2-chloroethanol, 2,2-dichloroethanol, 2-methoxyethanol, and trifluoroethanol were distilled before use. Ethylphosphonic acid was prepared by hydrolysis of the diethyl ester (Pfaltz and Bauer) by refluxing in 8 M HCl for 15 h. After solvent removal, a concentrated aqueous solution of the crude acid was neutralized to pH 5 with potassium hydroxide and evaporated to dryness. The crude monopotassium salt was recrystallized from methanol–ethanol. Glass-distilled water was used throughout.

Kinetics. The rates of decomposition of formaldehyde hydrate and formaldehyde hemiacetals were followed spectrophotometrically at 25 °C and ionic strength 1.0 M (KCl) by trapping the formaldehyde formed with hydrazine derivatives and following the increase in absorbance at the λ_{max} of the hydrazone.^{11,15} The trapping reagents used were thiosemicarbazide (275 nm, 0.01 M, pH 2.3–4.0), semicarbazide (240 nm, 0.001–0.01 M, pH 2.5–5.5), and hydrazine (235 nm, 0.01 M, pH 7.0–8.2). The concentrations of trapping reagents were such that there was no induction period in the observed pseudo-first-order rate plots (an induction period was observed at concentrations of trapping reagent and pH values at which trapping was not fast relative to formaldehyde hydration) and control experiments with double the concentration of trapping reagent were shown to give the same rate constants.

Stock solutions of hemiacetals and hydrate (0.05 M) were prepared by mixing 4 μL of 37% formaldehyde with 1 mL of the appropriate alcohol or water. These solutions were allowed to stand for at least 3 h before use, and were stable for several days, except for those made with chloroethanol and dichloroethanol. These two alcohols formed hemiacetals within minutes after mixing and plots of $\log \Delta$ absorbance against time became biphasic after about 4–6 h; therefore, these solutions were prepared fresh daily. No such biphasic plots were observed for at least two half-times in the experimental runs and the total absorbance change was constant for a series of runs, indicating that no significant formation of acetal had occurred in the stock solutions.

Kinetic runs were initiated by injecting 6 μL of hemiacetal or hydrate solution into 3 mL of reaction mixture to give a final concentration of 10^{-4} M. Stock solutions of trapping agents were adjusted to the pH of the buffer before use. Hydrochloric acid was used for pH control at pH values below 3.0. The ionic strength was maintained at 1.0 with potassium chloride. Pseudo-first-order rate constants, k_{obsd} , were obtained as the slopes of plots of $\ln \Delta A$ against time. All runs were linear for at least 2 (and usually for 3) half-lives. Values of the buffer-independent rate constants, k_0 , at high pH values were obtained from the intercepts of plots of k_{obsd} against the concentration of hydrazine buffers. Values of k_{cat} and k_0 were obtained from the slopes and intercepts of plots of k_{obsd} against buffer concentration. These plots were linear over the range 0.06–0.6 M buffer. Values of k_{HA} and k_{B} were determined from the intercepts of plots of k_{cat} against the fraction of the buffer in the basic form. All catalytic constants, Brønsted slopes, and structure–reactivity coefficients were calculated by the method of least squares.

Results

Figure 1 shows the dependence on pH of the pseudo-first-order rate constants (k_0), extrapolated to zero buffer concentration, for the breakdown of formaldehyde hydrate and ethyl, chloroethyl, and trifluoroethyl hemiacetals at 25 °C and ionic strength 1.0. The second-order rate constants for the acid

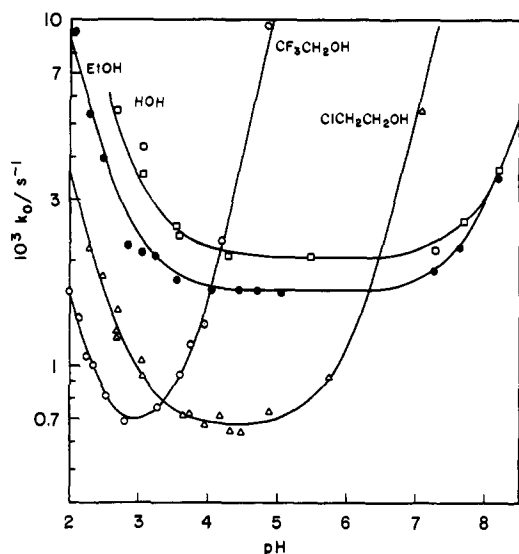


Figure 1. Dependence on pH of the hydrolysis of formaldehyde hydrate (□), ethyl hemiacetal (●), 2-chloroethyl hemiacetal (Δ), and trifluoroethyl hemiacetal (○) at ionic strength 1.0 (KCl), 25 °C. The k_0 values were obtained from the intercepts of plots of k_{obsd} against buffer concentration. Rate constants for the hydrate have been divided by a statistical factor of 2 for comparison with the hemiacetals.

Table I. Buffer-Independent Rate Constants for the Breakdown of Formaldehyde Hydrate and Hemiacetals (ROCH₂OH) at 25 °C and Ionic Strength 1.0 (KCl)

R	pK _{ROH} ^a	k_W , M ⁻¹ s ⁻¹ ^b	k_{OH} , M ⁻¹ s ⁻¹ ^c	k_H , M ⁻¹ s ⁻¹ ^d
CH ₃ CH ₂	16	2.93×10^{-5}	1.3×10^3	0.74
H	15.74	7.6×10^{-5}	2.1×10^3	2.84
CH ₃	15.54	3.27×10^{-5}	2.34×10^3	0.58
CH ₃ OCH ₂ - CH ₂	14.82	1.30×10^{-5}	5.5×10^3	0.43
ClCH ₂ CH ₂	14.31	1.18×10^{-5}	4.4×10^4	0.32
Cl ₂ CHCH ₂	12.89	9.1×10^{-6}	1.13×10^6	0.22
F ₃ CCH ₂	12.43	7.7×10^{-6}	1.1×10^7	0.12

^a Reference 19. ^b $k_W = k_0$ (at zero [H⁺], [OH⁻])/55.5. ^c In terms of antilog (pH - 14). ^d In terms of antilog (-pH).

(k_H), base (k_{OH}), and pH-independent (k_W) reactions were obtained from the slopes and intercepts of plots of these rate constants (k_0) against hydrogen ion and hydroxide ion activity and are presented in Table I. The lines in Figure 1 are calculated from these rate constants; the pseudo-first-order rate constants for the breakdown of trifluoroethyl hemiacetal in the absence of buffer, for example, are described by

$$k_0 \text{ (s}^{-1}\text{)} = 0.12a_{H^+} + 55.5 \times 7.7 \times 10^{-6} + 1.1 \times 10^7 a_{OH^-} \quad (5)$$

The k_W term accounts for 70% of k_0 at the pH-rate minimum for this compound and this value of k_W is, accordingly, less accurate than those for other compounds that exhibit a more significant pH-independent reaction (Figure 1).

The breakdown is also catalyzed by the acid and basic species of buffers (Figure 2). The catalytic constants based on total buffer concentration and the rate constants k_{HA} and k_B for general acid and general base-catalysis are summarized in Table II. Rate constants for cleavage of the hydrate and the methyl hemiacetal show satisfactory agreement with earlier data that were obtained under slightly different conditions.^{11,15}

Derived Equilibrium and Rate Constants. The acid dissociation constants and proton transfer steps for formaldehyde hemiacetals and hydrate are described by eq 6.

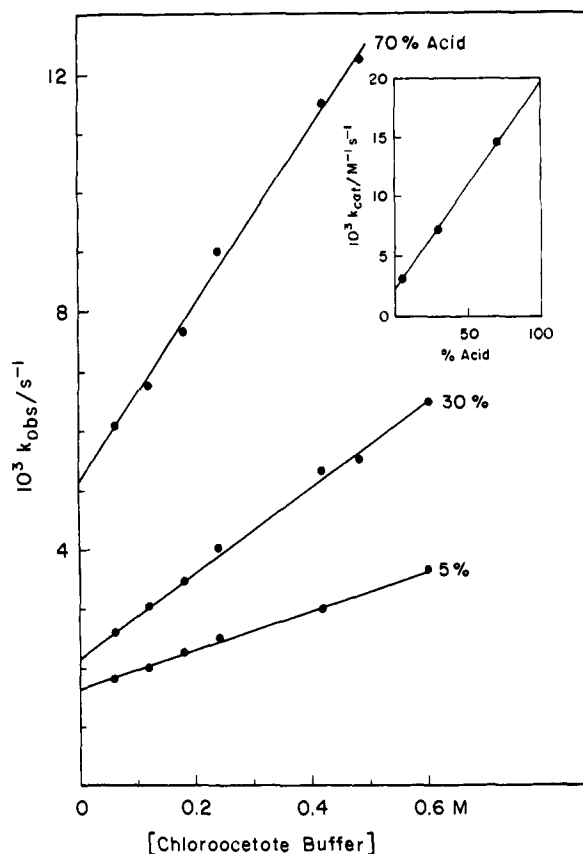
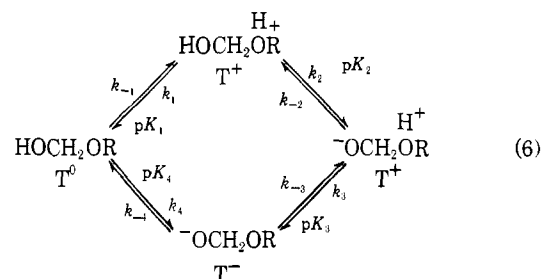


Figure 2. Plots of k_{obsd} against buffer concentration for the hydrolysis of formaldehyde ethyl hemiacetal in chloroacetate buffers, 5, 30, and 70% acid at 25 °C, ionic strength 1.0 (KCl). Inset: dependence of k_{cat} on the buffer composition.



pK₄. The dissociation constant of formaldehyde hydrate¹⁷ is given by $pK_4 = 13.27$. Other dissociation constants were calculated as described previously,¹⁸ based on a statistically corrected value of $pK_4 = 13.57$ for formaldehyde hydrate. Values of pK_4 for formaldehyde hemiacetals were calculated from the pK_a values of the parent alcohols¹⁹ with a fall-off factor of 0.21¹⁸ and range from 13.56 for the ethyl hemiacetal to 12.85 for trifluoroethyl hemiacetal.

pK₁. The (statistically corrected) pK_4 for HOCH₂OH of 13.57 is 2.0 units lower than the pK_a of methanol of 15.54.¹⁹ Assuming the same substituent effect for an HO group on pK_1 the (statistically corrected) value of pK_1 is -4.0 for the hydrate, based on a pK_a of -1.98 for the conjugate acid of methanol;²⁰ allowing for the two hydroxyl groups gives $pK_1 = -3.7$. The value of pK_1 for the ethyl hemiacetal is -4.6, based on the pK_a of -2.60 for methyl ethyl ether²⁰ and again allowing 2.0 pK units for the effect of the added hydroxyl group. Assuming the same substituent effects as for the ionization of the alcohols,¹⁹ pK_1 for the trifluoroethyl hemiacetal is then -8.3.

pK₂. Based on an electrostatic effect of $pK_4 - pK_2 = 4.7$ for the effect of the positive charge in T⁺ on the ionization of the hydroxyl group,^{21,22} the values of pK_2 are 8.9, 8.9, and 8.2 for

Table II. Acid and Base Catalysis of the Breakdown of Formaldehyde Hydrate and Hemiacetals (ROCH₂OH) at 25 °C and Ionic Strength 1.0 (KCl)

catalyst	fraction acid	$10^3 k_{\text{cat}}$, M ⁻¹ s ⁻¹	$10^3 k_{\text{HA}}$, M ⁻¹ s ⁻¹	$10^3 k_{\text{B}}$, M ⁻¹ s ⁻¹	catalyst	fraction acid	$10^3 k_{\text{cat}}$, M ⁻¹ s ⁻¹	$10^3 k_{\text{HA}}$, M ⁻¹ s ⁻¹	$10^3 k_{\text{B}}$, M ⁻¹ s ⁻¹
R = CH ₃ CH ₂					methoxyacetic acid	0.05	1.98	5.9	1.73
cyanoacetic acid	0.01	1.9	30.2	1.51		0.30	2.9		
	0.10	4.2				0.70	4.67		
	0.35	11.6			3-chloropropionic acid	0.08	3.70	4.33	3.58
chloroacetic acid	0.05	3.1	19.7	2.15		0.50	3.82		
	0.30	7.2				0.90	4.30		
	0.70	14.5			acetic acid	0.10	4.05	1.71	4.33
methoxyacetic acid	0.10	4.07	14.8	2.89		0.50	3.06		
	0.30	6.7				0.90	1.95		
	0.70	11.1			R = ClCH ₂ CH ₂				
3-chloropropionic acid	0.08	4.95	11.9	4.3	cyanoacetic acid	0.01	1.02	15.5	0.69
	0.70	9.6				0.05	1.46		
	0.95	11.8				0.20	3.83		
acetic acid	0.10	6.9	6.7	6.9	chloroacetic acid	0.05	1.46	9.7	0.98
	0.30	6.9				0.50	4.23		
	0.70	6.8				0.70	7.1		
R = H					methoxyacetic acid	0.05	1.62	3.90	1.95
cyanoacetic acid	0.01	5.8	108	5.0		0.30	2.63		
	0.10	15.7				0.70	3.32		
	0.20	25.4			3-chloropropionic acid	0.01	3.07	2.99	3.03
chloroacetic acid	0.05	8.6	71	6.3		0.08	3.03		
	0.30	25.3				0.50	3.00		
	0.50	38.5			acetic acid	0.30	3.83	1.47	4.85
methoxyacetic acid	0.10	11.6	43.8	7.8		0.70	2.49		
	0.30	17.6				0.95	1.63		
	0.70	33.7			R = Cl ₂ CHCH ₂				
3-chloropropionic acid	0.08	15.0	42.2	12.4	cyanoacetic acid	0.01	0.67	6.3	0.56
	0.50	27.5				0.20	2.18		
	0.90	39.3				0.35	2.53		
acetic acid	0.10	19.7	22.6	19.8	chloroacetic acid	0.10	1.43	5.1	0.93
	0.70	20.8				0.30	2.13		
	0.90	21.8				0.70	3.90		
R = CH ₃					methoxyacetic acid	0.10	2.63	2.04	2.73
cyanoacetic acid	0.01	1.83	26.3	1.8		0.30	2.64		
	0.04	2.80				0.70	2.15		
	0.35	10.4			3-chloropropionic acid	0.11	4.85	1.0	5.3
chloroacetic acid	0.05	4.07	23.1	3.05		0.50	3.63		
	0.10	5.07				0.90	1.46		
	0.30	8.6			acetic acid	0.30	7.6	0.75	10.9
methoxyacetic acid	0.10	4.85	13.4	4.25		0.50	5.9		
	0.30	7.3				0.95	1.26		
	0.70	10.2			R = CF ₃ CH ₂				
3-chloropropionic acid	0.08	6.5	9.0	6.3	cyanoacetic acid	0.01	1.02	2.88	1.03
	0.50	7.8				0.20	1.37		
	0.90	8.7				0.35	1.69		
acetic acid	0.10	9.2	5.1	9.6	chloroacetic acid	0.05	2.10	1.78	1.87
	0.50	7.3				0.30	1.66		
	0.90	5.7				0.70	1.82		
R = CH ₃ OCH ₂ CH ₂					methoxyacetic acid	0.30	3.47	0.83	4.63
cyanoacetic acid	0.01	0.95	17.1	0.71		0.70	2.02		
	0.10	2.17				0.95	0.99		
	0.35	6.4			3-chloropropionic acid	0.08	9.8	0.90	10.4
chloroacetic acid	0.05	1.89	11.3	1.24		0.50	5.9		
	0.10	2.19				0.90	1.70		
	0.50	6.4			acetic acid	0.70	8.0	0.35	26.3
					0.90	3.43			
					0.98	0.65			

the hydrate, ethyl hemiacetal, and trifluoroethyl hemiacetal, respectively.

pK₃. From the requirement that $pK_1 + pK_4 - pK_2 = pK_3$ the values of pK_3 are 0.7, 0.1, and -3.6 for the hydrate, ethyl hemiacetal, and trifluoroethyl hemiacetal, respectively (Table III).

The rate constant k_4 for the removal of a proton from HO-CH₂OR by water to form T⁻ + H⁺ (Table III) was calculated from $k_4 = k_{-4}K_4$, assuming a value of $k_{-4} = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$.²³

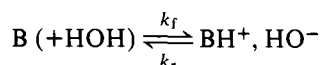
The rate constant k_4' for the removal of a proton by cyanoacetate anion (B) to form T⁻ was calculated from $k_4' = k_{-4}'K_4/K_{\text{BH}}$, in which K_{BH} is the dissociation constant of BH and assuming a value of $k_{-4}' = 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for the protonation of T⁻ by cyanoacetic acid²³ (Table III).

The rate-determining step for the base-catalyzed reaction in the breakdown direction according to the mechanism of eq 3 is the reaction of BH⁺ and T⁻ with the rate constant $k_{\text{BH}} = k_{\text{B}}K_{\text{BH}}/K_4$. Values of k_{BH} for the cyanoacetate- and water-

catalyzed reactions are shown in Table III; values for other bases are smaller.

The overall rate constant for the formation of T^\pm , from the hydrate or hemiacetal through the lower pathway of eq 6 with rate-determining protonation of T^- by cyanoacetic acid, is given by $k_{-3}K_4/K_{BH} = k_3'K_4/K_3$ (Table III); k_3' for the deprotonation by cyanoacetate of T^\pm , a relatively strong acid, is taken²⁴ to be $10^{10} \text{ M}^{-1} \text{ s}^{-1}$. (For the trifluoroethyl hemiacetal the formation of T^\pm by reaction of T^- with the proton is faster than with any buffer acid.)

The rate constant k_{-BH} for the cyanoacetate-catalyzed hydration of free formaldehyde (eq 3) is $11 \text{ M}^{-1} \text{ s}^{-1}$, based on $k_{-BH} = k_B/K_h$ in which k_B is the experimental rate constant for dehydration of the hydrate and $K_h = 4.4 \times 10^{-4} = [\text{HCHO}]/[\text{HOCH}_2\text{OH}]$ is the equilibrium constant for dehydration of the hydrate.²⁵ The first-order rate constant k_f for the removal of a proton from water by cyanoacetate ion to form hydroxide ion



is 0.017 s^{-1} , based on $k_f = k_r K_w/K_{BH}$ and assuming that $k_r = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$. The second-order rate constant k_f' for the removal of a proton from water adjacent to formaldehyde (based on a standard state of 1 M) is $0.017/55.5 = 3.1 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, 3.5×10^4 smaller than k_{-BH} .

The rate constant k_{-BH} for the cyanoacetate-catalyzed reaction of ethanol with free formaldehyde (Table III) is given by $k_{-BH} = k_B/K_{ROH}$, in which $K_{ROH} = [\text{HCHO}][\text{EtOH}]/[\text{HOCH}_2\text{OEt}] = 1.1 \times 10^{-3} \text{ M}$. This value of $K_{ROH} = K_h'/K_E$ was obtained from $K_h' = 55.5 K_h = 2.2 \times 10^{-2} \text{ M}$ and a reported value^{15b,26} of $K_E = [\text{HOCH}_2\text{OEt}][\text{HOH}]/[\text{EtOH} \cdot \text{HOCH}_2\text{OH}] = 21$ (at 20°C , based on molar concentrations of all reactants). The rate constant $k_{-B'}$ for the attack of hydroxide or ethoxide ion on free formaldehyde catalyzed by cyanoacetic acid according to the mechanism of eq 4 is given by $k_{-B'} = k_{-BH}K_{BH}/K_{ROH}$ (Table III). The value of $k_{-B'}$ for the proton-catalyzed attack of hydroxide ion on free formaldehyde is $9.7 \times 10^{14} \text{ M}^{-2} \text{ s}^{-1}$, based on a value of $k_{-BH} = 55.5 k_w/K_h = 9.7 \text{ s}^{-1}$ for the hydration of formaldehyde in water.

The first step of the *acid-catalyzed reaction* is the protonation of the leaving alcohol or hydroxyl group for the mechanism of eq 1 in the breakdown direction. The rate constant k_{-1}' for protonation of the trifluoroethyl hemiacetal by acetic acid is $1.2 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, based on $k_{-1}' = k_1'K_{HA}/K_1$ and assuming a value of $k_1' = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ for the diffusion-controlled reaction of acetate ion with the protonated hemiacetal.²⁴ The rate constant for protonation of the hydrate by water is $k_{-1} = 2.1 \times 10^{-8} \text{ s}^{-1}$, which is much smaller than the observed rate constant for pH-independent dehydration. However, the rate constant for protonation by the solvated proton is $k_{-1}' = 1.2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, assuming a value of $k_1' = 55.5 \times 10^{10} = 5.5 \times 10^{11} \text{ s}^{-1}$; this gives a rate constant for protonation of $\geq 1.2 \times 10^{-2} \text{ s}^{-1}$ up to pH 10, which would be more than adequate to account for the observed reaction rate. Similarly, the rate constant of $k_1' = 2.8 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for protonation of the trifluoroethyl hemiacetal by the proton is more than adequate to account for the pH-independent breakdown over the pH range in which this pathway is significant.

The second step of the acid-catalyzed cleavage reaction according to the mechanism of eq 1 is the reaction of T^+ and A^- with the rate constant $k_A = k_{HA}K_1/K_{HA}$. Values of k_A are given in Table III for reactions catalyzed by the proton, carboxylic acids, and water, which represent reactions of T^+ with water, carboxylate ions, and hydroxide ion, respectively, in this step.

The rate constants k_2 for the dissociation of the hydroxyl group of $\text{HOCH}_2\text{ORH}^+$ to form the zwitterionic intermediate

Table III. Calculated Equilibrium and Rate Constants for Reactions of Formaldehyde Hydrate and Hemiacetals^a

	HOCH ₂ OH	HOCH ₂ OEt	HOCH ₂ O- CH ₂ CF ₃
pK ₁	-3.7	-4.6	-8.3
pK ₂	8.9	8.9	8.2
pK ₃	0.7	0.1	-3.6
pK ₄	13.27	13.56	12.85
k ₂ (HOH) ^b	12.6	12.6	63
k _{2'} (CNAC) ^c	213	213	1070
k ₋₃ 'K ₄ /K _{BH} (Ac) ^c	2.7 × 10 ⁻³	3.5 × 10 ⁻⁴	3.5 × 10 ⁻⁷
k ₄ ^b	5.4 × 10 ⁻⁴	2.7 × 10 ⁻⁴	1.4 × 10 ⁻³
k _{4'} (CNAC) ^c	9.1 × 10 ⁻³	4.6 × 10 ⁻³	2.3 × 10 ⁻²
k _{BH} (CNAC) ^c	5.5 × 10 ⁸	3.2 × 10 ⁸	4.3 × 10 ⁷
(H ⁺) ^c	7.8 × 10 ¹⁰	5.8 × 10 ¹⁰	3.0 × 10 ⁹
k _{-BH} (CNAC)	11 ^c	1.4 ^d	
k _{-B'} (CNAC) ^d	7.4 × 10 ¹²	8.5 × 10 ¹³	
k _A (HOH) ^b	1.4 × 10 ⁴	2.9 × 10 ⁴	2.2 × 10 ⁷
(CNAC) ^c	8.8 × 10 ⁴	2.0 × 10 ⁵	9.1 × 10 ⁷
(Ac) ^c	4.8 × 10 ⁶	1.2 × 10 ⁷	2.9 × 10 ⁹
(OH ⁻) ^c	2.0 × 10 ¹⁵	6.4 × 10 ¹⁵	7.7 × 10 ¹⁸
k _A (Ac)	57 ^c	6.4 ^d	0.078 ^d
(CNAC)	270 ^c	29 ^d	0.64 ^d
(H ⁺)	7100 ^c	705 ^d	27 ^d
k _{-HA} (Ac) ^e	1.6 × 10 ⁹ ^c	1.8 × 10 ⁸ ^d	2.2 × 10 ⁶ ^d
(CNAC) ^e	2.9 × 10 ⁷ ^c	3.1 × 10 ⁶ ^d	6.8 × 10 ⁴ ^d
(H ⁺) ^e	4.5 × 10 ⁶ ^b	4.4 × 10 ⁵ ^c	1.7 × 10 ⁴ ^c

^a The rate and equilibrium constants are defined in eq 1-4 and 6, and the text. ^b s⁻¹. ^c M⁻¹ s⁻¹. ^d M⁻² s⁻¹. ^e Lower limits, assuming pK₀ = -2.8.

T^\pm are given by $k_2 = k_{-2}K_2$ and have been calculated assuming a value²³ of $k_{-2} = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ (Table III). The values of k_2' for the same reaction with a buffer base are given by $k_2' = k_{-2}'K_2/K_{HA}$ and were calculated assuming a value²³ of $k_{-2}' = 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (Table III).

The rate constants for the acid-catalyzed addition of ROH to free formaldehyde (eq 1) are given by $k_{-A} = k_{HA}/K_{ROH}$ (Table III). The equilibrium constant K_{ROH} has been defined above in the description of the rate constant for the base-catalyzed addition reaction, k_{-BH} ; a preliminary value of $K_E = 4.9$ for the trifluoroethanol reaction²⁶ was used for these calculations.

The individual rate constants for the acid-catalyzed addition reaction according to the mechanism of eq 2 cannot be calculated because the dissociation constant for protonated formaldehyde, K_0 , is not known. However, limits may be set on these rate constants based on the known pK₀ for the dissociation of protonated acetone of -2.8;²⁷ the pK₀ of protonated formaldehyde is expected to be more negative than this value. The rate constants k_0' for the protonation of formaldehyde by cyanoacetic and acetic acids are $\leq 9.3 \times 10^4$ and $\leq 3.5 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$, respectively, based on $k_{-0}' = k_0'K_{HA}/K_0$ and assuming that $k_0' = 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ and $K_0 = 10^{2.8}$. The rate constant k_{-0} for protonation of formaldehyde by the proton is $\leq 8.7 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, based on $k_{-0} = k_0/K_0$ and assuming that $k_0 = 55.5 \times 10^{10} = 5.5 \times 10^{11} \text{ s}^{-1}$.

Lower limits for the rate constant k_{-HA} for the general-base-catalyzed attack of ROH on protonated formaldehyde according to the mechanism of eq 2 were calculated from $k_{-HA} = k_{-A}/K_0$ for the proton-catalyzed reaction and $k_{-HA} = k_{-A}K_{HA}/K_0$ for the buffer-catalyzed reactions (Table III).

Calculated rate constants for reactions with protonated carbonyl compounds require the use of pK_a values based on the correct acidity function for the compound under consideration; earlier calculations based on H_0 values for half-protonation generally give rate constants that are too large.

The intermediates in the hydroxide ion catalyzed reactions are stable enough to have significant, though short, lifetimes. The rate constants k^- for breakdown of the anionic intermediates T^- are given by $k^- = k_{OH}K_w/K_4$ and range from 390

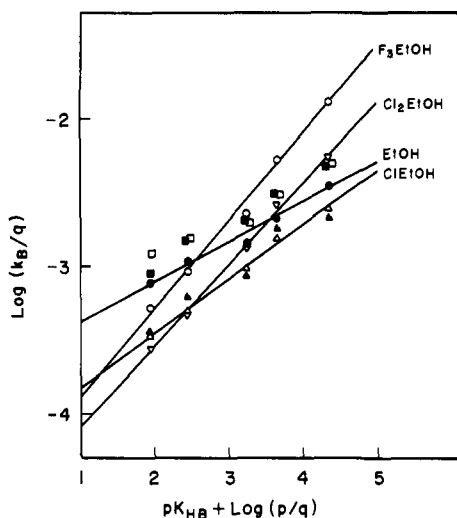


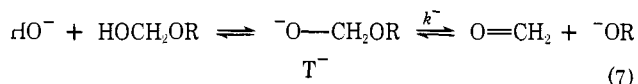
Figure 3. Brønsted plots for general base catalysis of the cleavage of formaldehyde hydrate, \square ; ethyl hemiacetal, \bullet ; methyl hemiacetal, \blacksquare ; methoxyethyl hemiacetal, \blacktriangle ; chloroethyl hemiacetal, \blacktriangle ; dichloroethyl hemiacetal, ∇ ; and trifluoroethyl hemiacetal, \circ . Lines are drawn through the points for only the ethyl, chloroethyl, dichloroethyl, and trifluoroethyl hemiacetals. The rate constants for the hydrate have been corrected by an additional statistical factor of 2.

Table IV. Brønsted α , β , and β_{1g} Values for General Base and General Acid Catalysis of the Breakdown of Formaldehyde Hemiacetals (ROCH₂OH)^a

R	pK _{ROH}	β	α
CH ₃ CH ₂	16	0.26	0.28
H	15.74	0.24	0.29
CH ₃	15.54	0.26	0.27
CH ₃ OCH ₂ CH ₂	14.82	0.34	0.33
ClCH ₂ CH ₂	14.31	0.34	0.33
Cl ₂ CHCH ₂	12.89	0.54	0.36
F ₃ CCH ₂	12.43	0.58	0.36

catalyst	pK _{BH}	β_{1g}^{Bb}	$\beta_{1g}^{HA^c}$
acetate	4.65	-0.10	0.32
2-chloropropionate	3.93	-0.03	0.26
methoxyacetate	3.40	0.00	0.34
chloroacetate	2.70	0.10	0.26
cyanoacetate	2.23	0.11	0.27
H ⁺	-1.74		0.20

^a The structure-reactivity coefficients are calculated by the method of least squares. ^b For general base catalysis relative to catalysis by methoxyacetate, based on the slopes of the lines in Figure 5b. ^c For general acid catalysis.



s^{-1} for the hydrate to $8 \times 10^5 s^{-1}$ for the trifluoroethyl hemiacetal. The rate constants for attack of hydroxide and ethoxide ions on formaldehyde of 4.8×10^6 and $1.3 \times 10^8 M^{-1} s^{-1}$, respectively (calculated from k_{OH} and the equilibrium constants of the reactions), are below the diffusion-controlled limit, so that there must be a significant barrier for the addition of RO^- to formaldehyde in the encounter complex. However, these large rate constants mean that there would be no barrier for the attack of alkoxide ions on protonated formaldehyde. The rate constant $k_A = 1.4 \times 10^4 s^{-1}$ that accounts for the observed rate of the proton-catalyzed reaction through rate-determining breakdown of the protonated intermediate T^+ (Table III) means that this intermediate has a significant lifetime.

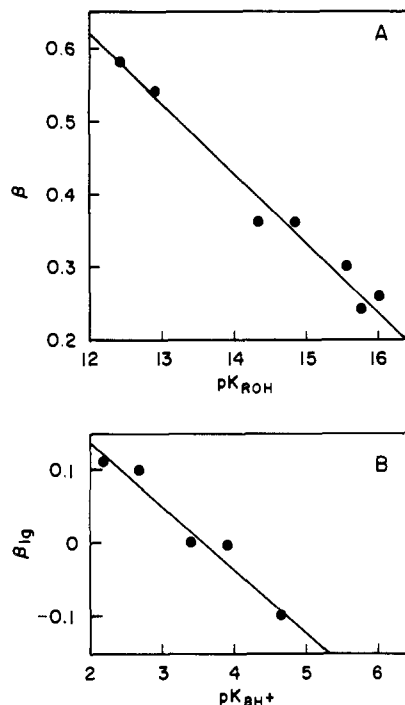


Figure 4. (A) Dependence of the Brønsted β coefficient on the pK of the leaving group for general base catalysis of the cleavage of formaldehyde hemiacetals. (B) The change in β_{1g} , normalized to the rate constants for catalysis by methoxyacetate (Figure 5B), with changing pK_{BH}.

Discussion

General Base Catalysis. We first consider the question of which of the two kinetically equivalent mechanisms (eq 3 and 4) for the observed (kinetic) general base catalysis is correct. The class n mechanism of eq 3 involves true general base catalysis of the addition of the nucleophilic reactant, alcohol or water, to formaldehyde and general acid catalysis of the breakdown of the anion of the addition compound in the reverse direction (the direction that was examined in the experiments reported here). The class e mechanism of eq 4 involves true general base catalysis in the breakdown direction and general acid catalysis of the addition of the conjugate base of ROH to formaldehyde, the electrophilic reactant, in the addition direction.

Brønsted plots for general base catalysis of the cleavage of formaldehyde hydrate and hemiacetals are shown in Figure 3. The plots show a jumble of points and crossing lines for reasons that will be described shortly. Lines are drawn through only the points for cleavage of the ethyl, chloroethyl, dichloroethyl, and trifluoroethyl hemiacetals, in the interest of clarity, but the trends shown by these compounds are generally followed for the other leaving groups. Two conclusions are apparent.

(1) The Brønsted slopes, β , increase with increasing acidity of the leaving alcohol (Table IV). A plot of β against the pK_a of the leaving group (Figure 4A) gives a slope of $\partial\beta/\partial\text{pK}_{1g} = p_{xy}' = 0.095$.

(2) There is a tendency for the Brønsted lines to cross, such that the most acidic alcohols are most reactive with the most basic catalysts and the weakly acidic alcohol leaving groups are most reactive with the weakly basic catalysts. Thus, dichloroethanol is next to the most reactive leaving group for acetate catalysis and the least reactive for cyanoacetate catalysis; trifluoroethanol leaves most rapidly with acetate catalysis, at an intermediate rate for cyanoacetate catalysis, and is the poorest leaving group for the "water" reaction (Table I). The rate constants for water as a leaving group (open

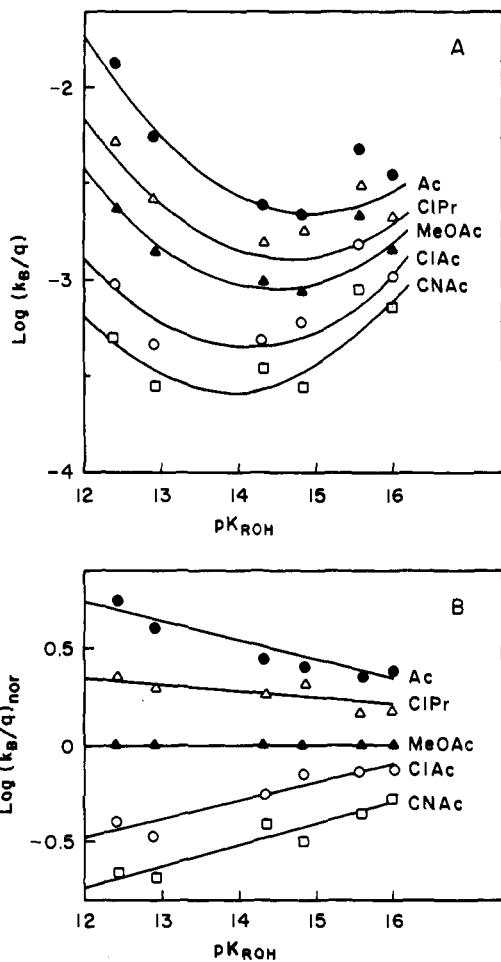


Figure 5. Dependence of $\log k_B$ on the pK of the leaving alcohol for the cleavage of formaldehyde hemiacetals, based on observed values of k_B (A) and on normalized values of $k_{B(\text{obsd})}/k_{B(\text{methoxyacetate})}$ (B). The solid lines in A were calculated from eq 14. The lines, from top to bottom, refer to catalysis by acetate, chloropropionate, methoxyacetate, chloroacetate, and cyanoacetate anions.

squares, Figure 3) have been corrected by a statistical factor of 2, to allow for the two modes of cleavage of the hydrate to give formaldehyde, and are very similar to those for methanol (closed squares). Water and methanol are both slightly better leaving groups than ethanol, perhaps because of a steric effect.

The dependence of the rate on the pK of the leaving group follows a curved line for each of the catalysts, with a positive deviation of the point for the methyl hemiacetal (Figure 5A). It is apparent from Figure 5 that the apparent jumble of points in the Brønsted plots of Figure 3 actually represents well-ordered behavior that arises from this nonlinear dependence of the rate on the pK of the leaving group. The curvature of the lines in Figure 5A is such that the slope, β_{1g} , increases with increasing pK of the leaving group. This corresponds to an "anti-Hammond" effect for the leaving group with a negative sign for the coefficient²⁸ $\partial\beta_{1g}/-\partial pK_{1g} = p_{y'} = -0.20$. The effect of the base strength of the catalyst on the sensitivity of the reaction to the pK of the leaving group is not readily seen in Figure 5A but is apparent in Figure 5B, in which the catalytic constants are plotted relative to those for methoxyacetate. Figure 5B shows that there is a tendency for β_{1g} to increase with decreasing pK of the catalyst so that the sign of the interaction coefficient $\partial\beta_{1g}/-\partial pK_{BH^+} = p_{xy'}$ is positive. This is required by the reciprocal relationship²⁸⁻³⁰

$$\frac{\partial\beta}{-\partial pK_{1g}} = \frac{\partial\beta_{1g}}{-\partial pK_{BH^+}} = \frac{1}{C_5} = p_{xy'} \quad (8)$$

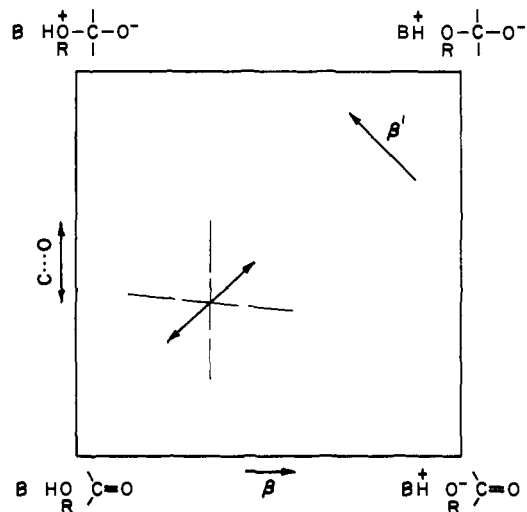


Figure 6. Reaction coordinate energy diagram for the base-catalyzed reactions of alcohols and water with formaldehyde according to the mechanism of eq 3, with proton transfer along the horizontal coordinate, C-O bond formation and cleavage along the vertical coordinate, and charge development on the leaving group, measured by β' (β_{nuc} or β_{1g}), along a diagonal coordinate; the energy contour lines are omitted. Level lines of constant energy through a saddle point are shown as dashed lines and a reaction coordinate is drawn bisecting these lines, as described in the text.

since $\partial\beta/\partial pK_{1g}$ has already been shown to be positive. The changes in β_{1g} with changing pK of the catalyst fit a line of slope $\partial\beta_{1g}/-\partial pK_{BH^+} = 0.087$ (Figure 4B), which agrees satisfactorily with the value of $\partial\beta/\partial pK_{1g} = 0.095$ obtained from Figure 4A.

This pattern of structure-reactivity behavior provides strong support for the class n mechanism of eq 3, with true general base catalysis of the addition of water and alcohols to formaldehyde. This is the same mechanism that has been suggested previously for this reaction.^{3,5} In the breakdown direction this mechanism involves cleavage of the conjugate base of the addition compound, $ROCH_2O^-$, with catalysis by the conjugate acid of the catalyst, BH^+ , which appears experimentally as the kinetically equivalent general base catalysis of breakdown of the uncharged addition compound. Closely similar structure-reactivity behavior has been observed previously for alcohol expulsion to form a phthalimidium ion,³¹ for the cleavage of substituted-phenyl acetals,³² for the breakdown of alcohol addition compounds of an imine,³³ and for the cleavage of ortho esters.³⁴ These reactions all involve general acid catalysis of alcohol or water expulsion from an electrophilic center, analogous to the mechanism of eq 3, and are kinetically unambiguous or of proved mechanism. An increase in β with electron-withdrawing substituents has also been observed for the mutarotation of substituted sugars catalyzed by three substituted pyridines, for which Capon has assigned a class n reaction mechanism on the basis of a calculated rate constant greater than the diffusion-controlled limit for the ring closure step of the alternative class e mechanism.³⁵

The structure-reactivity behavior of these reactions can be rationalized qualitatively by the three-dimensional reaction coordinate diagram^{30,36} of Figure 6, in which the amount of proton transfer is indicated by the horizontal coordinate and the amount of C-O bond formation and cleavage by the vertical coordinate; the energy contour lines have been omitted. An electron-donating substituent on the alcohol will stabilize the protonated alcohol and lower the energy of the upper left relative to that of the lower right corner of the diagram. The position of the transition state will then tend to slide downhill toward the upper left corner (perpendicular to the reaction coordinate). The horizontal axis of the diagram describes the

amount of proton transfer, as measured by the Brønsted β value, so that this shift represents a decrease in β , as observed; in the reverse, breakdown direction it represents an increase in the amount of proton transfer from BH^+ in the transition state. Similarly, an increase in the acidity of BH^+ will raise the energy of the right relative to the left side of the diagram and will tend to shift the position of the transition state upward (this shift is the resultant of a downhill movement perpendicular to the reaction coordinate and an uphill movement parallel to the reaction coordinate²⁸). This upward shift corresponds to an increased positive charge development on the alcohol oxygen atom in the transition state and in β_{1g} , as observed (β_{1g} and β_{nuc} follow a diagonal axis and range from negative values in the lower right to positive values in the upper left part of the diagram, as indicated by β' in the figure).

The shift of the transition state toward the upper left corner with electron-donating substituents on the leaving alcohol also corresponds to a shift toward a more cationic oxygen atom on the leaving alcohol in the transition state (an "anti-Hammond" effect). This explains the observed increase in β_{1g} with decreasing $\text{p}K_{1g}$ and the upward curvature in the plots of $\log k$ against $\text{p}K_{1g}$. The observed increase in the rate of leaving group expulsion with increasing $\text{p}K$ of basic alcohols, corresponding to a positive β_{1g} , is itself diagnostic of a class n reaction mechanism in which there is proton donation to the leaving alcohol. Alcohol expulsion without such proton donation, as in a class e mechanism, would be aided by electron-withdrawing substituents that stabilize the leaving oxy anion.

The observed structure-reactivity behavior is the opposite of that expected for the class e mechanism of eq 4.^{28,30} According to this mechanism electron-donating substituents on the leaving group are expected to increase the Brønsted β value and increasing base strength of the catalyst is expected to increase β_{1g} , with a positive value of p_{xy} according to the relationship

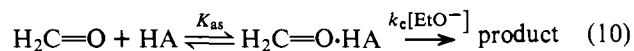
$$\frac{\partial \beta}{\partial \text{p}K_{1g}} = \frac{\partial \beta_{1g}}{\partial \text{p}K_{\text{HA}}} = p_{xy} \quad (9)$$

This behavior has been observed for the kinetically unambiguous, reversible addition of thiol anions to acetaldehyde³⁷ and also accounts for the observed structure-reactivity data for the acid-catalyzed formation and breakdown of formaldehyde hemiacetals.

The absolute rate constants for the individual steps of the reaction according to the mechanisms of eq 3 and 4 may be calculated from the observed rate constants and estimated ionization constants (eq 6, Table III). These rate constants are consistent with the class n mechanism of eq 3 but rule out the class e mechanism of eq 4 because rate constants larger than the diffusion-controlled limit are required to account for the observed rate constants. The calculated rate constant for the removal of a proton from the hydrate by a buffer base to form T^- in the first step of the reaction, according to the mechanism of eq 3, is $k_4' = 9.1 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ for cyanoacetate ion, which is just adequate to account for the observed rate constant of $k_B = 5 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$. The ratio k_4'/k_B is larger for other bases and for the hemiacetals. There is no requirement for a one-encounter mechanism⁸ in which the catalyst abstracts a proton and catalyzes the breakdown of T^- before diffusing away, although such a mechanism might be required for weaker bases than cyanoacetate. The largest rate constant for the reaction of BH^+ with T^- in the second step of this mechanism is $k_{\text{BH}} = 5.5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ for the cyanoacetate-catalyzed reaction, which is below the diffusion-controlled limit.

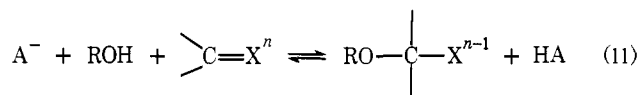
The rate constants for the reverse, base-catalyzed addition of water or alcohol to formaldehyde may be calculated from the equilibrium constants and observed rate constants for the reaction. The rate constant for the general-acid-catalyzed

attack of ethoxide ion on formaldehyde, the second step of the reaction according to the class e mechanism of eq 4, may then be calculated from the ionization constants of ethanol and the catalyst and is $k_{-B}' = 8.5 \times 10^{13} \text{ M}^{-2} \text{ s}^{-1}$ for the cyanoacetate-catalyzed reaction (Table III). The second-order rate constant for the reaction of ethoxide ion with an encounter complex of the acid and formaldehyde



is then given by $k_e = k_{-B}'/K_{\text{as}} = 8.5 \times 10^{14} \text{ M}^{-1} \text{ s}^{-1}$, assuming a value of $K_{\text{as}} = 0.1 \text{ M}^{-1}$. This value of k_e is larger than the diffusion-controlled limit and provides further evidence against the mechanism of eq 4. This result is another example supporting the generalization that the reaction of strongly basic nucleophiles with reactive carbonyl compounds is not subject to general acid catalysis.

The absolute rate constant for formaldehyde hydration in water of approximately 10 s^{-1} is similar to the value of 56 s^{-1} for the hydration of a phthalimidium ion,³¹ consistent with the very similar behavior of the two reactions. However, the rate constant for the expulsion of methanol from the phthalimidium addition compound catalyzed by acetic acid³¹ is $5.3 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$, which is 10^{10} slower than the corresponding rate constant of $k_{\text{BH}} = 4.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for cleavage of the anion of formaldehyde methyl hemiacetal. The acid-catalyzed cleavage reactions represent the reverse of the base-catalyzed or uncatalyzed ($\text{A}^- = \text{HOH}$) addition reactions (eq 11) and



similar differences exist for comparisons of the addition of alcohols and the expulsion of alcohols catalyzed by other acids, including the proton. These large differences reflect, at least in part, an electrostatic effect that favors oxygen protonation and RO^- expulsion from the hemiacetal anion, relative to the neutral phthalimidium addition compound, and favors the equilibrium addition of alcohols to the phthalimidium cation (eq 11, $n = +1$) relative to uncharged formaldehyde ($n = 0$).³⁸

General Acid Catalysis. A choice between the kinetically equivalent class e mechanism of eq 1 and the class n mechanism of eq 2 for the observed (kinetic) general acid catalysis may be made from the structure-reactivity behavior and other characteristics of the reaction.

The Brønsted plots for general acid catalysis of the cleavage of formaldehyde hemiacetals and hydrate (Figure 7) exhibit a slower rate and a small but definite increase in α as the $\text{p}K$ of the leaving group decreases. Plots of the ratios of the rate constants for cleavage of the hydrate and the hemiacetals (Figure 8A) show more clearly that there is a change in slope and a plot of α against the $\text{p}K$ of the leaving alcohol has a slope of $\partial \alpha / \partial \text{p}K_{1g} = p_{xy} = 0.022$ (Figure 8B). The lines in Figure 7 are drawn with slopes calculated from this p_{xy} coefficient. The rate constants for cleavage of the hydrate are slightly faster than those for the hemiacetals even after correction by a statistical factor of 2, confirming earlier results of Le Hénaff for the methyl hemiacetal.¹⁵ Plots of $\log k$ against the $\text{p}K$ of the leaving group (not shown) give slopes in the range of $\beta_{1g} = 0.20-0.34$ (Table IV). There is an irregular but definite decrease in β_{1g} with increasing strength of the catalyzing acid, as is required by the data shown in Figures 7 and 8A and by the reciprocal relationship²⁸⁻³⁰

$$\frac{\partial \alpha}{\partial \text{p}K_{1g}} = \frac{\partial \beta_{1g}}{\partial \text{p}K_{\text{HA}}} = \frac{1}{c_2} = p_{xy} \quad (12)$$

The following evidence demonstrates that the general-acid-catalyzed reaction proceeds according to the class e

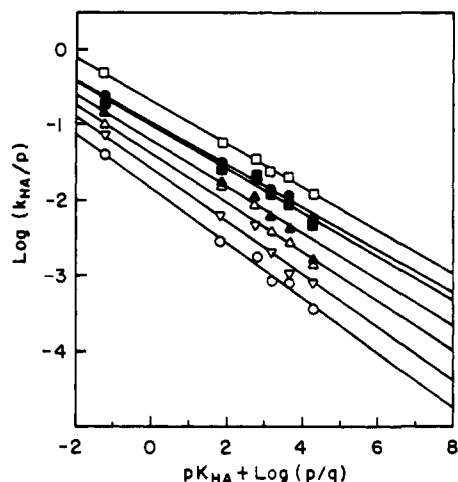


Figure 7. Brønsted plots for general acid catalysis of the cleavage of formaldehyde hydrate, \square ; ethyl hemiacetal, \bullet ; methyl hemiacetal, \blacksquare ; methoxyethyl hemiacetal, \blacktriangle ; chloroethyl hemiacetal, \triangle ; dichloroethyl hemiacetal, ∇ ; and trifluoroethyl hemiacetal, \circ . The slopes of the lines are drawn based on a coefficient $p_{xy} = \partial\alpha / -\partial pK_{1g} = 0.022$.

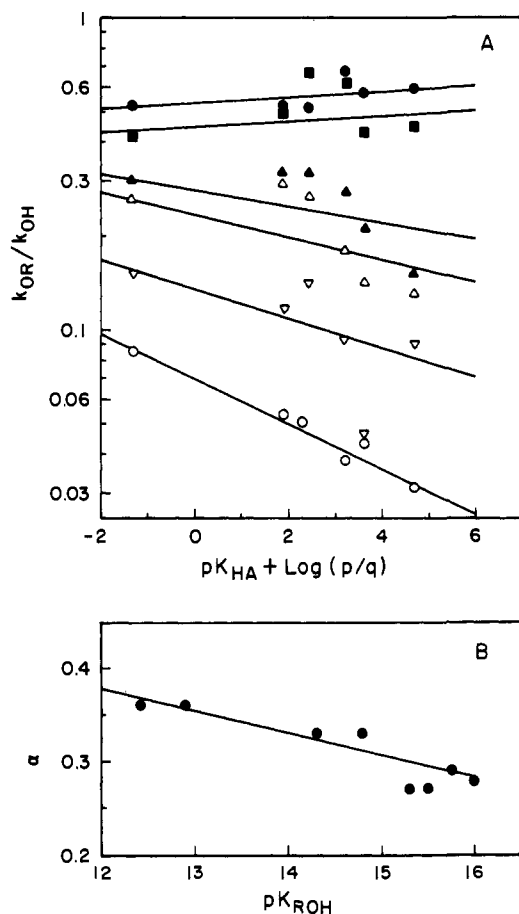


Figure 8. (A) Brønsted plots showing rate constants for general acid catalysis of hemiacetal cleavage normalized to those for the hydrate. (B) Dependence of the Brønsted coefficient α for general acid catalysis on the pK of the leaving group.

mechanism of eq 1 and not the class n mechanism of eq 2, in agreement with earlier suggestions.^{3,5,10}

(1) The observed structure-reactivity interactions are consistent with the mechanism of eq 1. The three-dimensional reaction coordinate diagram for this mechanism²⁸ is shown in Figure 9 with the Brønsted α coefficient for proton transfer

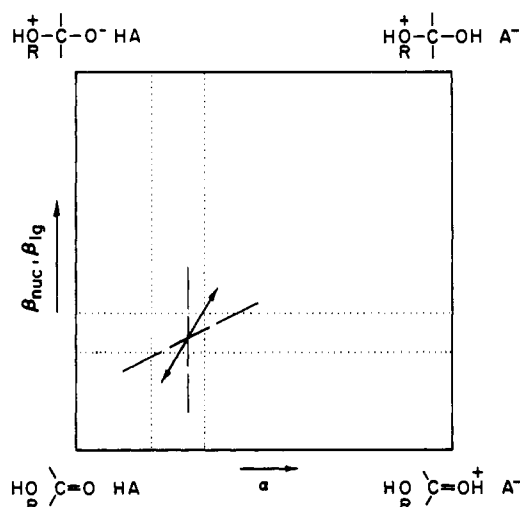


Figure 9. Reaction coordinate energy diagram for the acid-catalyzed reactions of alcohols and water with formaldehyde according to the mechanism of eq 1, with proton transfer along the horizontal coordinate defined by α and C-O bond formation and cleavage along the vertical coordinate defined by β_{nuc} or β_{1g} ; the energy contour lines are omitted. Level lines of constant energy through a saddle point are shown as dashed lines and a reaction coordinate is drawn bisecting these lines, as described in the text. The dotted lines indicate the observed range of variation of structure-reactivity parameters and transition state structure.

along the horizontal coordinate and the β_{1g} (or β_{nuc}) coefficient for C-O bond cleavage or formation along the vertical coordinate; the energy contour lines are omitted. An electron-withdrawing substituent that decreases the pK of the leaving group (or nucleophile) raises the energy of the top relative to the bottom of the energy diagram and thereby shifts the position of the transition state toward the upper right (parallel to the reaction coordinate) and toward the lower right (perpendicular to the reaction coordinate). The resulting shift to the right corresponds to an increase in α and in the amount of proton transfer in the transition state for the weaker nucleophile, as observed. However, the alternative assignment of the mechanism of eq 2 is not, in principle, excluded by the experimental data. A reaction coordinate for this mechanism with an important vertical component is expected to show the opposite structure-reactivity interaction, but a reaction coordinate with a predominant horizontal component will give the observed increase in α with decreasing pK of the leaving group (this corresponds to a negative value of the coefficient p_{xy} of eq 8 and a positive curvature c' of the transformed energy diagram for this mechanism).²⁸

Stronger evidence for the assignment of the class e mechanism of eq 1 comes from an empirical comparison with the observed structure-reactivity interactions for reactions of known mechanism. A number of unambiguous class n reactions involving true general acid catalysis of leaving group expulsion have been shown to exhibit a decrease in α with electron-withdrawing substituents in the leaving alcohol³¹⁻³⁴ and there is no obvious reason why the cleavage of hemiacetals should not exhibit the same behavior if it proceeded through a class n mechanism. On the other hand, there is precedent for an increase in α with decreasing pK of the nucleophile-leaving group in the general-acid-catalyzed reaction of thiol anions with acetaldehyde, a class e reaction.³⁷ The values of α increase from ≤ 0.10 to 0.26 as the pK of the nucleophile is decreased from 10.25 to 2.68 in this reaction, giving a p_{xy} coefficient of 0.026. In the hemiacetal reaction the values of α increase over the range 0.27 to 0.36 as the nucleophile-leaving group decreases in basicity with a similar p_{xy} value of 0.022 (the values of α are the same for the two directions of the reaction). The conjugate acids of the alcohol nucleophiles have pK values

below zero and these α values appear to follow the trend set by the more basic thiol anion nucleophiles.

The sign of the p_{xy} coefficient in these reactions is opposite to that expected from a direct electrostatic effect; however, an electrostatic effect is unlikely to be significant for end atom interactions in any case.²⁸ The larger value of α for hydration than for the addition of basic nucleophiles to the carbonyl group (which often exhibit $\alpha = 0$) was used earlier as an argument favoring a class e reaction mechanism of general acid catalysis.³⁹ However, this argument should not be applied to nucleophiles of grossly different structure unless it can be shown that the observed general acid catalysis does not represent a trapping mechanism and that "water" reactions with $\alpha = 0$ do not represent uncatalyzed or base-catalyzed reactions.⁴⁰

The values of β_{1g} for the acid-catalyzed reactions, in the range 0.20 to 0.34, are all positive (Table IV). This is consistent with the class e mechanism of eq 1 and may be accounted for by protonation of the leaving alcohol in an initial equilibrium step followed by a large amount of C–O bond cleavage in the transition state; in the addition direction this corresponds to a moderately early transition state for alcohol attack without proton removal that results in a moderate amount of positive charge development on the attacking oxygen atom. The positive β_{1g} values that show a small increase with increasing pK of the catalyst are not inconsistent with a class n reaction mechanism, in principle,²⁸ but class n reaction mechanisms ordinarily exhibit a decrease in β_{1g} with increasing pK of the catalyst that eventually leads to a negative value of β_{1g} , as in the base-catalyzed formaldehyde reactions and other reactions.^{31–34}

(2) The most direct evidence for the mechanism of eq 1 is the fact that the rate constant for the proton-catalyzed cleavage of formaldehyde methyl hemiacetal ($0.58 \text{ M}^{-1} \text{ s}^{-1}$) is 2600 times larger than that for the cleavage of formaldehyde dimethyl acetal ($2.2 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$).⁴¹ The dimethyl acetal is a model for the mechanism of eq 2 in which a (fixed) methyl group replaces the (mobile) proton of the hemiacetal. The much larger rate constant for the hemiacetal shows that the acetal is not a satisfactory model for the correct reaction mechanism and suggests that removal of the proton of the hemiacetal in the transition state is responsible for a large rate increase, as in the mechanism of eq 1. This rate difference may be contrasted with the rate difference of about tenfold for the acid-catalyzed cleavage of acetophenone-bisulfite addition compounds compared with the corresponding *O*-methyl compounds.⁴² This reaction is believed to proceed through a class n mechanism and the relatively small rate difference may reasonably be ascribed to a solvation effect. Similarly, the difference of less than tenfold in the rates of acid-catalyzed dehydration of HONHCH(OH)Ar and HON(CH₃)CH(OH)Ar suggests that there is little or no cleavage of the N–H bond of the former compound in the transition state.⁴³ It is possible that a larger rate difference could be observed because of more favorable solvation of the transition state leading to $\text{H}_2\text{C}=\text{OH}^+$ than of that leading to $\text{H}_2\text{C}=\text{OMe}^+$ if the transition state for the mechanism of eq 2 occurred very late along the reaction coordinate; however, this possibility is ruled out by the relatively small Brønsted coefficients of $\alpha = 0.27$ – 0.36 , and the positive β_{1g} values of 0.20–0.34, which are inconsistent with a late transition state with a large amount of C–O bond cleavage for this mechanism.

(3) If the mechanism of eq 2 is correct, acetal cleavage is a model for hemiacetal cleavage and the two reactions should exhibit similar values of α . However, the cleavage of ordinary aliphatic acetals exhibits catalysis only by the proton, presumably through specific acid catalysis with $\alpha = 1.0$, whereas the formaldehyde hemiacetals exhibit general acid catalysis with $\alpha = 0.25$ – 0.35 .^{39,44} Furthermore, the observed values of

$\alpha = 0.25$ – 0.35 for the hemiacetal reaction are smaller than the observed values of $\alpha = 0.5$ – 1.0 for the cleavage of other acetals that do show general acid catalysis and for related reactions that proceed according to the mechanism of eq 2.^{31–34,45}

(4) The observed Brønsted coefficients for the general-acid-catalyzed reaction are shifted in the opposite direction from that expected for the mechanism of eq 2, when compared with the Brønsted coefficients for the general-base-catalyzed reaction. The observed Brønsted coefficients of $\beta = 0.24$ – 0.58 for the general-base-catalyzed cleavage of formaldehyde hemiacetals correspond to α values of $1 - \beta = 0.42$ – 0.76 for general acid catalysis of the breakdown of the hemiacetal anion, T^- , in the rate-determining step of the class n mechanism that has been assigned to this reaction (eq 3). The class n mechanism of eq 2 is the same as that of eq 3 except that a proton is added to the carbonyl oxygen atom. The addition of this proton to the oxy anion and to the carbonyl group will stabilize the top relative to the bottom of the reaction coordinate diagram for this mechanism (Figure 6) and should therefore increase α by shifting the position of the transition state toward the lower left and the upper left corners, in directions parallel and perpendicular to the reaction coordinate, respectively. This is inconsistent with the observed values of $\alpha = 0.27$ – 0.36 for the general-acid-catalyzed reaction, which are lower than 0.42–0.76.

(5) The observed rate constants are not consistent with calculated rate constants for the steps of the acid-catalyzed reaction according to the mechanism of eq 2. (a) The addition of ROH to formaldehyde according to the mechanism of eq 2 requires first the protonation of formaldehyde with the rate constant k_{-0} , followed by the general-base-catalyzed attack of ROH on formaldehyde with the rate constant $k_{-\text{HA}}$. The calculated value of $k_{-0} \leq 350 \text{ M}^{-1} \text{ s}^{-1}$ for acetic acid is only sixfold larger than the value of $k_{-\text{A}} = 57 \text{ M}^{-1} \text{ s}^{-1}$ for the hydration reaction catalyzed by acetic acid (Table III). The value of k_{-0} is based on a pK_0 of -2.8 for protonated acetone and, since K_0 for protonated formaldehyde is expected to be larger than this and k_{-0} correspondingly smaller, it is unlikely that the rate of formaldehyde protonation is fast enough to account for the hydration reaction through the mechanism of eq 2.

(b) The rate constant $k_{-\text{HA}}$ that is required to account for the acetate-catalyzed hydration of protonated formaldehyde according to the mechanism of eq 2 is $\geq 1.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, based on $pK_0 = -2.8$ (Table III). Since the true K_0 is almost certainly larger than this, the required $k_{-\text{HA}}$ will also be larger and the mechanism will be excluded by a requirement for a step that exceeds the diffusion-controlled limit. A still larger value of $k_{-\text{HA}} \geq 1.3 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$ would be required to account for a previously reported catalytic constant for boric acid¹¹ according to the mechanism of eq 2.

The calculated rate constants for the individual steps are adequate to account for the reaction according to the mechanism of eq 1. The rate constant $k_{-1}' = 1.2 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$ for protonation of the trifluoroethyl hemiacetal by acetic acid to form T^+ is larger than the observed rate constant of $k_{\text{HA}} = 3.5 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ and the ratio k_{-1}'/k_{HA} is larger for other buffer acids and hemiacetals. The rate constants k_{A} for acetate-catalyzed cleavage of the protonated substrate in the second step are 4.8×10^6 and $1.2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for the hydrate and ethyl hemiacetal, respectively (Table III), and the corresponding rate constants for other catalysts are smaller. However, the value of $k_{\text{A}} = 2.9 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for the acetate-catalyzed breakdown of protonated trifluoroethyl hemiacetal is at the borderline of the diffusion-controlled limit and it is possible that this reaction proceeds through a one-encounter mechanism,⁸ in which acetic acid protonates the hemiacetal and acetate ion then catalyzes its breakdown before diffusing away.

The "Water" Reaction. The following evidence shows that

the pH-independent, "water-catalyzed" reactions of formaldehyde hydrate and hemiacetals represent largely or entirely general base rather than general acid catalysis by water.

(1) The observed rate constants for catalysis by water are larger than those predicted by the Brønsted plots for general acid catalysis by factors of 5–100, with the largest deviation for the trifluoroethyl hemiacetal. They also exhibit a much smaller spread, covering a range of only fourfold compared with the range of 200-fold expected by extrapolation of the Brønsted plot for general acid catalysis (Figure 7) to the pK of water. In contrast, the observed rate constants fall close to the extrapolated Brønsted lines for general base catalysis. The rate constants are two to four times smaller than predicted by the Brønsted lines for the hemiacetals of weakly acidic alcohols; for dichloroethyl and trifluoroethyl hemiacetals the observed rate constants fall above the Brønsted lines by factors of less than 2, which is smaller than the uncertainty of the extrapolation. Thus, general base catalysis by water *should* occur at rates equal to or greater than the observed rates, but general acid catalysis of the observed magnitude is not expected. However, the difference between the rate constants for the two mechanisms is not large for the compounds with weakly acidic leaving groups and it is not unlikely that the general-acid-catalyzed mechanism is favored for other, related reactions.

The structure of water permits it to act as a proton donor and acceptor simultaneously in a bifunctional, cyclic mechanism of catalysis. The fact that there is no significant positive deviation of the points for catalysis by water above the Brønsted line for general base catalysis by carboxylate anions, which cannot act as bifunctional catalysts, shows that such bifunctional catalysis does not provide a significant advantage for catalysis by water. However, this does not exclude a cyclic, one-encounter mechanism for water.

(2) General acid catalysis by water according to the mechanism of eq 1 requires that the breakdown reaction proceed through formation of the protonated hydrate or hemiacetal, T^+ , followed by reaction of this intermediate with hydroxide ion with the rate constant k_A . The values of k_A required to account for the observed rate range from $2.0 \times 10^{15} \text{ M}^{-1} \text{ s}^{-1}$ for the hydrate to $7.7 \times 10^{18} \text{ M}^{-1} \text{ s}^{-1}$ for the trifluoroethyl acetal (Table III). These values are much larger than the diffusion-controlled limit and therefore rule out this mechanism.

The rate constant k_4 for the removal of a proton from the hydrate by water to form separated T^- and H_3O^+ is $5.4 \times 10^{-4} \text{ s}^{-1}$ (Table III), which is eight times smaller than the observed rate constant for the water reaction. The differences for the hemiacetals are smaller. The rate constants k_{BH} for the recombination of H_3O^+ with T^- and cleavage to formaldehyde in the second step of the mechanism of eq 3 range from 3.0×10^9 to $7.8 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ (Table III). These rate constants are adequate or nearly adequate to account for the water reaction according to the mechanism of eq 3, without exceeding the diffusion-controlled limit. If the larger values are correct, the reactions of the hydrate and ethyl hemiacetal presumably proceed through a one-encounter mechanism in which H_3O^+ donates a proton to T^- before separating from T^- , thus avoiding the diffusion-controlled steps.⁸ Alternatively, the equilibrium constants utilized for the calculations have an uncertainty such that the rate constants may be at the diffusion-controlled limit; this would provide an explanation for the negative deviations of several rate constants for the water reactions below the Brønsted lines for general base catalysis.

These conclusions differ from those of Bell and Evans for the dehydration of formaldehyde hydrate, which were based on a better fit of the rate constant for the water reaction to the Brønsted line for general acid than for general base catalysis.¹¹ Our data would not permit a conclusion based on the data for the hydrate alone, but the data for the substituted hemiacetals

provide a much better fit to the Brønsted lines for general base catalysis. There are also differences between the Brønsted slopes of $\alpha = 0.24$ and $\beta = 0.40$ reported by Bell and Evans¹¹ and our values of $\alpha = 0.29$ and $\beta = 0.24$ for the hydrate. The principal difference between the two sets of data is that the former comprises a larger range of pK values but also a larger range of structural variation of the catalysts; there is generally fair to good agreement between individual rate constants obtained in the two studies. The catalytic constants for carboxylic acids in Table II are consistently higher than those reported earlier,¹¹ possibly because of the higher salt concentration in the present study; however, there is good agreement between the rate constants for catalysis by the proton in the two studies. We do not know whether the differences in Brønsted slopes represent curvature in the Brønsted correlations or differences in the activity of different structural classes of catalysts.

Hydroxide Ion Catalysis. General base catalysis by hydroxide ion through a concerted mechanism is not expected to be significant because such catalysis requires a driving force that arises from an initially unfavorable proton transfer to or from the catalyst that becomes favorable during the course of the reaction; this does not occur with hydroxide ion catalysis.⁴⁶ Since the hemiacetal is more acidic than water, almost every encounter of hydroxide ion with the hemiacetal will give water and the hemiacetal anion. It is not reasonable that the reaction should then occur through a thermodynamically unfavorable reprotonation by water to give a less reactive species followed by concerted proton transfer and alkoxide ion expulsion, because the driving force for leaving group expulsion in the concerted reaction with partial proton removal is smaller than in the original hemiacetal anion with a completely removed proton. Similarly, there is no advantage to a concerted mechanism in the direction of hemiacetal or hydrate formation because proton transfer from the alcohol or water to hydroxide ion will be fast and reprotonation, of trifluoroethoxide ion by water, for example, followed by concerted attack of ROH with partial proton removal should have less driving force than the direct attack of the anion.

Ritchie has suggested that hydroxide ion attack may represent general base catalysis by hydroxide ion of the addition of water because of the unfavorable solvation energy of a hydroxide ion adjacent to the substrate.⁴⁷ This implies that alkoxide ions should also catalyze the attack of water on formaldehyde; in the reverse direction this represents catalysis by alcohol of HO^- expulsion. However, this mechanism is not significant for the reactions examined here because the structures of the starting hemiacetals and products establish that expulsion of alkoxide ion must occur; the reverse, addition reaction must also exist.

It is unlikely that there is concerted catalysis by water of proton donation to the leaving alkoxide ion because a plot of $\log k_{OH}$ (Table I) against the pK of the leaving alcohol has a slope of $\beta_{1g} = -1.1$. This shows that the transition state of these reactions closely resembles the alkoxide ion product and suggests that there has been little or no proton transfer to the leaving alkoxide ion in the transition state. In contrast, the reactions that are believed to proceed with concerted proton transfer to the leaving group from stronger acid catalysts according to the mechanism of eq 3 exhibit much less negative, or even positive, values of β_{1g} (Table IV).

Catalysis by rate-determining proton transfer is not significant because such reactions are close to diffusion controlled in the favorable direction and the rate constants for hydroxide ion catalyzed breakdown and formation of the hemiacetals are smaller than diffusion controlled (Table I; the rate constant k_f for hydroxide ion attack on formaldehyde is given by $k_{OH}/K_{eq} = 4.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$).

The rate constants for the hydroxide ion catalyzed reactions fall about two orders of magnitude above the extrapolated

Brønsted plots for general base catalysis by other bases. This is also consistent with the conclusion that the hydroxide ion reactions involve a different mechanism, i.e., specific base catalysis with direct expulsion and addition of alkoxide ions and some degree of solvation by water of the developing negative charge in the transition state. Extrapolation of the β_{1g} data for other base catalysts to the pK of water, based on the coefficient $p_{xy} = \partial\beta_{1g}/-\partial pK_{BH} = 0.09$, gives $\beta_{1g} = -1.1$ for the hydroxide ion catalyzed reaction. This is consistent with a shift of the transition state almost all of the way toward the lower right corner of Figure 6 so that the reaction proceeds by a stepwise mechanism through the alkoxide ion intermediate in this corner.

It is of interest that the large β_{1g} of -1.1 implies a late transition state for alkoxide ion expulsion and a small value of β_{nuc} with a correspondingly *early* transition state for the reverse, addition reaction, whereas the dependence of the rate of hydroxide ion addition on polar substituents in a series of benzaldehydes substituted with electron-withdrawing substituents is almost the same as that for the equilibrium addition reaction, implying a very *late* transition state.⁴⁸ This difference is almost certainly too large to be accounted for by a "Hammond effect" and probably represents another example of imbalance in the extent to which different processes have taken place in the transition state, which is manifested by imbalance of the substituent effects in different parts of the reactants. Very similar results have been reported previously for the attack of alkoxide ions on esters, thiol esters, and carbon acids, and for the expulsion of alkoxide ions from $RNHCH(Ar)OR'$ to form imines; in these reactions the substituent effects on the alkoxide suggest that there is almost a full negative charge on the oxygen atom whereas substituent effects on the rest of the molecule and other data show that there is a considerable amount of bonding to this oxygen atom in the transition state.⁴⁹ The difference can be accounted for, at least in large part, if it is assumed that the alkoxide ion must lose some solvation in order to attack the electrophile and, conversely, that the negative charge on the leaving alkoxide ion is incompletely solvated in the transition state. The resulting excess negative charge will make β_{1g} more negative in the breakdown direction and decrease β_{nuc} in the attack direction.⁴⁹

Transition State Characterization. General Base Catalysis. The characteristics of the general-base-catalyzed reactions with formaldehyde are now becoming familiar and appear to represent a general mechanism for catalysis of the addition and expulsion of alcohols and water when the electrophilic reactant has some degree of stability.³¹⁻³⁴ This characteristic behavior suggests that the proton transfer to or from the oxygen atom of the alcohol (or water) molecule is concerted with cleavage or formation of the C-O bond, in the sense that there is no indication for the existence of any high-energy metastable intermediates, and that there appears to be motion of all reacting atoms in the transition states of these reactions. This reaction pathway is generally accompanied by an additional pathway involving the expulsion of alkoxide or hydroxide ion, for which general acid-base catalysis by water provides little or no thermodynamic advantage; the rate constant for this uncatalyzed pathway usually exhibits a positive deviation from Brønsted plots. We will describe the characteristics of the general-base-catalyzed reaction with respect to the absolute values of structure-reactivity coefficients, the lifetimes of the intermediates that would be required for a stepwise mechanism, the changes in structure-reactivity coefficients with changes in the structure of reactants and catalysts, and a quantitative description of the transition state in terms of a three-dimensional reaction coordinate energy diagram.

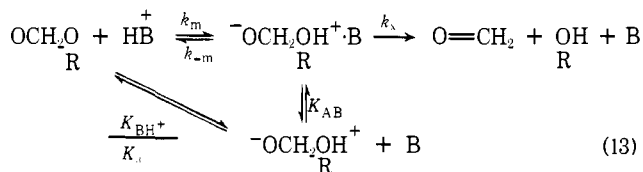
The structure-reactivity data provide the simplest of the several lines of evidence supporting a concerted (as opposed to a stepwise) reaction mechanism. The observed Brønsted β

values of 0.24–0.58 for the formaldehyde reaction correspond to values of $\alpha = 1 - \beta$ that span the range 0.42–0.76 for general acid catalysis of the breakdown of the hemiacetal anion according to the mechanism of eq 3. This range of α values is difficult to rationalize by a stepwise or double potential well hydrogen-bonding mechanism; it suggests a large, but certainly not complete, transfer of the proton in the transition state. The α values are not inconsistent with a mechanism in which the proton is in a single well hydrogen bond in the transition state, but such a mechanism does not involve stepwise proton transfer and is therefore concerted. The large range of β_{1g} from negative to positive values requires that there must also be cleavage of the carbon-oxygen bond in the transition state. The reversal in the sign of β_{1g} suggests that the charge on the leaving oxygen atom can be either positive or negative, depending on the balance between the amounts of proton transfer and C-O bond cleavage in the transition state. Such a change is also difficult or impossible to explain by a stepwise reaction mechanism.

The rate of breakdown upon encounter with an acid is faster than the rate of protonation of the leaving group for some or all of the anionic intermediates T^- , so that catalysis is enforced by the short or nonexistent lifetime of the dipolar intermediate T^\pm . This means that the reaction cannot proceed through a stepwise mechanism involving free T^\pm as an intermediate. It is consistent with a concerted mechanism in which the addition compounds of acidic alcohols fall apart with partial proton transfer because they cannot exist with full proton transfer. If T^\pm has a short or nonexistent lifetime for addition compounds of ROH and formaldehyde, it certainly does not exist for addition compounds of more stable carbonyl compounds, esters, and other acyl compounds, so that a concerted mechanism of general acid-base catalysis of water or alcohol addition and expulsion will be enforced for these compounds also. Nonexistence of this intermediate provides a possible explanation for the fact that catalytic constants for water and for stronger bases fall on the same Brønsted line in a number of reactions, such as general-base-catalyzed ester hydrolysis, in which there is little or no thermodynamic advantage for proton transfer to water and concerted catalysis would otherwise not be expected.⁴⁶

The nonexistence of T^\pm as a free intermediate is most certain for the trifluoroethyl hemiacetal, for which the calculated rate constant for proton transfer to form T^\pm in the acetate-catalyzed reaction is $k_{-3}' K_4/K_{BH} = 3/5 \times []^{-7} M^{-1} s^{-1}$ (Table III). This is nearly 10^5 slower than the observed rate constant of $2.6 \times 10^{-2} M^{-1} s^{-1}$. Similarly, the rate constant $k_f' = 3.1 \times 10^{-4} M^{-1} s^{-1}$ for the removal of a proton by cyanoacetate ion from water adjacent to a formaldehyde molecule is 3.5×10^4 smaller than the rate constant of $k_{-BH} = 11 M^{-1} s^{-1}$ for the cyanoacetate-catalyzed hydration of formaldehyde. This suggests that the proton transfer is made possible by the increase in the acidity of the attacking water molecule as it forms a bond to the carbonyl carbon atom in a concerted mechanism. In the breakdown reaction, proton transfer is made possible by the increase in electron density on the leaving oxygen atom that is brought about by partial C-O bond cleavage.

It has been noted above that the observed rate constants, k_w , for the water reaction correspond to rate constants, k_{BH} , at the diffusion-controlled limit for the proton-catalyzed breakdown of T^- , so that the lifetime of T^\pm must be very short even for the hydrate. The rate constant that would be required for rate-determining breakdown of T^\pm in the water reaction of the trifluoroethyl hemiacetal is $k_t = 55k_w K_3/K_4 = 1.1 \times 10^{13} s^{-1}$; if $k_3 \geq 10k_t$, in order that k_t be rate determining, $k_3 \geq 10^{14} s^{-1}$. Alternatively, the proton transfer in the breakdown of the trifluoroethyl hemiacetal could occur within an encounter complex to form an intermediate that is stabilized by hydrogen bonding and breaks down to products in a subsequent rate-determining step (k_x) before the catalyst diffuses away (eq 13).



Assuming that $k_{-m} > 10k_x$ in order for k_x to be rate determining, k_{-m} is $>4.4 \times 10^{14} \text{ s}^{-1}$ for $\text{HB}^+ = \text{HOAc}$, based on $k_x = k_B K_3 / K_{\text{AB}} K_4 = 4.4 \times 10^{13} \text{ s}^{-1}$ and estimating $K_{\text{AB}} = 17 \text{ M}^{-1}$ from an equation proposed by Hine.⁵⁰ Rate constants of this magnitude are not consistent with a stepwise mechanism with a significant barrier for the steps and provide further evidence that the reaction must be concerted. The proton transfer step itself cannot be rate determining because the rate of this step should be sharply decreased by electron-withdrawing substituents on the alcohol, but the rate constant for the proton transfer step that would be required to account for the observed rate constant is $k_{-3}' = k_B K_{\text{BH}} / K_4 = 1.8 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for the chloroethyl hemiacetal and $4.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ for the trifluoroethyl hemiacetal.

The changes in structure-reactivity parameters with polar substituents on the reactants provide further evidence for a concerted reaction mechanism. The large change in β with changing $\text{p}K$ of the alcohol and change in β_{1g} with changing $\text{p}K$ of the catalyst that are described by $p_{xy}' = \partial\beta / -\partial\text{p}K_{1g} = \partial\beta_{1g} / -\partial\text{p}K_{\text{BH}^+} = 0.09$ represent a coupling of the structure-reactivity parameters for the alcohol and the catalyst that suggests a coupling of the bond-making and -breaking processes of the catalyst and the alcohol in the transition state. A positive p_{xy}' coefficient can be caused by simple electrostatic interactions, without changes in the amount of bond formation and cleavage in the transition state,²⁸ but it is unlikely that the contribution of this electrostatic effect is larger than the value of $\tau = p_{xy}'$ (electrostatic) = 0.024 suggested by Hine.^{50,51}

In the simplest case the structure-reactivity relationships for the mechanism of eq 3 may be described by the three-dimensional energy diagram of Figure 6, which is defined in terms of the experimental structure-reactivity parameters β and β_{1g} (β').²⁸ The large p_{xy}' and p_y' coefficients may be accounted for qualitatively by a predominantly diagonal reaction coordinate on such a diagram, as described above. It should be noted that there is no evidence for an increase in the Brønsted α value with increasing strength of the catalyzing acid for this class of reactions (in the breakdown direction), although α does increase sharply with increasing basicity of the leaving alcohol. This is the behavior that is expected for a diagonal reaction coordinate of a concerted reaction (Figure 6); it would not be expected for a proton resting in a single potential well with only C-O bond cleavage occurring in the transition state, which would correspond to a vertical reaction coordinate in Figure 6.⁵¹

The change in β_{1g} with changing $\text{p}K$ of the leaving group, which is defined by $p_y' = \partial\beta_{1g} / -\partial\text{p}K_{1g} = -0.20$, is consistent with a concerted mechanism and cannot be accounted for by an electrostatic interaction effect without changes in bond length in the transition state. The magnitudes of $p_y' = -0.20$ and $p_{xy}' = 0.09$ are consistent with each other according to the relationship $p_y' = p_y - p_x - 2p_{xy}'$; there is no requirement for "Hammond effects" for the acid and carbonyl compound that give rise to significant p_x and p_y coefficients, respectively.^{28,51} There is suggestive evidence for a significant negative p_y' term in the upward curvature of plots of $\log k$ against $\text{p}K_{\text{ROH}}$ for the expulsion of alcohols from addition compounds of a phthalimidium ion³¹ and an imine³³ and in the sharp upward deviation of the rate constants for the cleavage of *p*-methyl- and *p*-methoxyphenyl methyl benzaldehyde acetals.^{32b}

A quantitative treatment of the structure-reactivity data is consistent with a reaction coordinate for the formaldehyde

reactions that is nearly diagonal on the diagram of Figure 6, in which the axis for β_{1g} (β') is diagonal; it is intermediate between horizontal and diagonal on a transformed diagram that is defined in terms of perpendicular axes for β_{1g} and the Brønsted β for proton transfer.²⁸ The values of $p_x = \partial\beta / -\partial\text{p}K_{\text{BH}^+} \approx 0$, $p_y' = -0.20$, and $p_{xy}' = 0.09$ give curvatures at the saddle point of $a = -1.2$ in the horizontal direction, $b = 0$ in the vertical direction, and $c = -11.1$ for the diagonal curvature. These curvatures give coordinate ratios of $g_1/g_2 = 0$ and -9.25 for the two lines of constant energy ("level lines") that pass through the saddle point, as shown by the dashed lines in Figure 6. A reaction coordinate that bisects these level lines at 48° from the vertical is also shown in the figure. For the transformed diagram (not shown) the curvatures are $a' = -12.3$, $b' = 0$, and $c' = -11.1$, and g_1/g_2 are 0 and -0.90 . This gives one vertical level line and one that is rotated -42° counterclockwise from the vertical ($\tan 42^\circ = 0.90$). A reaction coordinate that bisects the level lines is rotated 69° clockwise from the vertical.⁵²

The observed rate constants are described in terms of these structure-reactivity coefficients by²⁸

$$\begin{aligned}
 -\log k = & \frac{1}{2}p_x \text{p}K_{\text{BH}^+} + \frac{1}{2}p_y' \text{p}K_{1g}^2 \\
 & + p_{xy}' \text{p}K_{\text{BHP}} \text{p}K_{1g} - \beta_{0\text{p}} K_{\text{BH}} - \beta_{1g}^0 \text{p}K_{1g} + F \quad (14)
 \end{aligned}$$

The solid lines in Figure 5A are calculated from eq 14 based on these coefficients, $\beta_0 = 1.677$, $\beta_{1g}^0 = -2.583$, and $F = -12.075$. The calculated lines provide a satisfactory fit to the experimental data for the different catalysts and leaving alcohols, with the exception of methanol, which exhibits the previously mentioned positive deviation from structure-reactivity correlations.

It is not known, for both the base- and acid-catalyzed reactions, whether there is a water molecule between the catalyst and the substrate nor whether tunneling contributes to the motion of the proton in the transition state. Either or both of these factors would imply that the coupling process is more complex than is described by Figure 6, but probably would not alter the conclusion that the reaction mechanism is in some sense concerted.

If general base catalysis of the addition of water and alcohols to carbonyl compounds is expected for most such reactions, why is it not observed when a general acid catalyst is assisting the reaction by proton donation to the carbonyl group? Such a reaction would give rise to a term in the rate law that is second order in buffer concentration. The structure-reactivity diagrams illustrate one possible answer to this question. Proton donation to the carbonyl group makes the aldehyde more reactive and increases the energy of the bottom relative to the top of the diagram of Figure 6. This will tend to shift the position of the transition state perpendicular to the reaction coordinate toward the upper left corner and parallel to the reaction coordinate toward the lower left corner. The resultant shift corresponds to a decrease in β so that base catalysis becomes less significant relative to the water reaction; β eventually approaches zero. The same effect provides one reason that general acid catalysis is not seen for the decomposition of acetals that give rise to unstable oxocarbenium ions.^{36,53} The value of $\alpha = 1.0$ for these reactions corresponds to $\beta = 0$ for the reverse, addition reaction.

General Acid Catalysis. The acid-catalyzed reactions of water and alcohols with formaldehyde through the mechanism of eq 1 extend a trend in the series of acid-catalyzed carbonyl addition reactions that relates the mechanism of catalysis to the stability and basicity of the addition intermediate that would be formed in the absence of acid catalysis.^{6,37} With strongly basic nucleophiles and reactive carbonyl compounds this intermediate is frequently stable enough to abstract a proton from water before it reverts to reactants and acid catalysis is neither required nor observed, as in the addition of

Hine equation⁵⁰ the expected value of α for hydrogen bonding of acids to an intermediate T^\pm of $pK = 8.9$ is approximately 0.26. This number is not exact, but the value of α should be considerably smaller for hydrogen bonding to the less basic transition state than to T^\pm .

The structure-reactivity relationships illustrated by the diagram of Figure 9 provide one explanation of why bifunctional catalysis by bases as well as acids, giving a term second order in buffer concentration, is not observed for the acid-catalyzed reaction. As the pK of the nucleophile is increased the Brønsted α value decreases, according to the positive coefficient $p_{xy} = \partial\alpha / -\partial pK_{\text{nuc}}$. An increased pK of the nucleophile stabilizes the top relative to the bottom of the diagram so that the transition state is shifted perpendicular to the reaction coordinate toward the upper left corner and parallel to the reaction coordinate toward the lower left corner, resulting in the observed decrease in α . General base catalysis of the attack of ROH will effectively increase the basicity of the nucleophile by partial proton abstraction and this increased basicity will result in a decrease in α toward zero, so that general acid catalysis by buffers will become less significant relative to water and will eventually disappear.

The trend toward increasing Brønsted α values with decreasing basicity of the nucleophile for the attack of thiol anions³⁷ and alcohols, which is described by the positive p_{xy} coefficient for class e general acid catalysis, is also consistent with the large Brønsted α values of 1.0 and 0.5 for general acid catalysis of the addition of hydrogen peroxide to *p*-chlorobenzaldehyde⁵⁶ and acetone,⁵⁷ respectively, the α values of 0.38–0.40 for the reversible dimerization of dihydroxyacetone and glycolaldehyde,¹³ and the large α value for general acid catalysis of the addition of free thiols to acetaldehyde.⁵⁴ An increase in α with increasing stability of the carbonyl compound that is described by a positive p_{xy} coefficient for a class e reaction²⁸ may also contribute to these large α values and to the large α value of 0.54 for general acid catalysis of the hydration of acetaldehyde,¹² which is more stable than formaldehyde. These α values near 0.5 presumably represent a continuation of the trend toward a fully concerted reaction mechanism as the addition intermediate T^\pm becomes less stable with decreasing pK of the nucleophile and increasing stability of the electrophile.⁶

Choice of Catalytic Mechanism. We can provide partial answers to the question of why a class n mechanism is preferred for observed (kinetic) general base catalysis and a class e mechanism for observed (kinetic) general acid catalysis, compared with the alternative possible mechanisms. General acid and base catalysis occur in order to avoid the formation of highly unstable free intermediates and the transition states leading to their formation. Both kinds of catalysis avoid the formation of the dipolar addition compound T^\pm , which may be so unstable as to have no significant lifetime for hemiacetals of weakly acidic alcohols. General acid catalysis also avoids the formation of fully protonated formaldehyde, an unstable oxocarboxonium ion.

The choice of mechanism for *kinetic general base catalysis* may be ascribed to an avoidance of the most basic oxy anion intermediate.⁵⁸ A class n mechanism (eq 3) avoids the formation of the anion of the nucleophile and a class e mechanism (eq 4) avoids the formation of the anion of the addition compound. For water and the alcohols examined here the alkoxide anion is more basic than the anion of the hydrate or hemiacetal (Tables I and III) and it is reasonable that the preferred mechanism avoids the formation of the alkoxide ion. As the anion becomes less basic the relative basicities will be reversed and it is known that ethanethiol anion adds without catalysis and less basic thiols add with catalysis through a class e mechanism.^{37,54} The preferred mechanism is also reversed when the anion of the addition compound becomes more basic

and kinetic general base catalysis of the addition of ROH to imines occurs through a class e mechanism, i.e., general acid catalysis of the addition of RO^- .³³

The trend for the Brønsted β value to increase with decreasing pK of the nucleophile or leaving group (positive p_{xy} coefficient) is consistent with the reported values of $\beta = 0.66$ and 0.5 for general base catalysis of the reactions of hydrogen peroxide ($pK = 11.6$) with *p*-chlorobenzaldehyde⁵⁶ and acetone,⁵⁷ respectively, and $\beta \approx 0.8$ for cleavage of the dimers of dihydroxyacetone and glycolaldehyde,¹³ which probably proceed through a class n reaction mechanism. These values correspond to relatively small α values, in the range 0.2–0.5, for general acid catalysis of the breakdown of the anion of the addition compound. A continuation of this trend of increasing β with weaker nucleophiles (better leaving groups) will make general base catalysis less important relative to uncatalyzed addition of the conjugate base of the nucleophile (specific base catalysis). This is consistent with the fact that general base catalysis is rarely if ever observed for the addition of more acidic nucleophiles to carbonyl compounds.

A class n mechanism for *kinetic general acid catalysis* requires the formation of the $H_2C=OH^+$ ion (eq 2), whereas a class e mechanism avoids this intermediate but proceeds through the unstable T^+ ion (eq 1). The available data suggest that the oxocarboxonium ion $H_2C=OH^+$ is so unstable that general base catalysis of its hydration does not occur and that class n reaction mechanisms are only observed when the protonated electrophile is unusually stable. An extrapolation from the rate constants of up to $4 \times 10^8 \text{ s}^{-1}$ for the hydration of oxocarboxonium ions formed from acetophenone ketals suggests that there is little or no barrier for the addition of water to oxocarboxonium ions derived from formaldehyde.⁵⁹ If this is the case and the addition of ROH is diffusion controlled there cannot be buffer catalysis of the addition of ROH to $H_2C=OH^+$, as required by a class n mechanism, because the rate of diffusion is not increased by buffers. The slow rate of cleavage of formaldehyde acetals compared with hemiacetals provides empirical evidence that the pathway through an oxocarboxonium ion-like transition state is of higher energy than that for hemiacetal cleavage through a class e mechanism. There is evidence supporting a class n mechanism of general acid catalysis for the addition of bisulfite to substituted acetophenones, but this appears to be a special case involving a relatively stable protonated ketone and class n mechanisms are rare for general-acid-catalyzed carbonyl addition reactions.⁴² For additions of ROH to imines, which form a very stable protonated electrophile, class n mechanisms are common and class e mechanisms are unknown for general acid catalysis.

References and Notes

- (1) Supported in part by grants from the National Science Foundation (BM471-01501) and the National Institute of General Medical Sciences of the National Institutes of Health (GM 20888).
- (2) Department of Chemistry, Washington and Jefferson College, Washington, Pa. 15301.
- (3) R. P. Bell and W. C. E. Higginson, *Proc. R. Soc. London, Ser. A*, **197**, 141 (1949).
- (4) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5224 (1963).
- (5) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964).
- (6) W. P. Jencks, *Acc. Chem. Res.*, **9**, 425 (1976).
- (7) R. P. Bell, *Adv. Phys. Org. Chem.*, **4**, 1 (1966).
- (8) M. Eigen, *Discuss. Faraday Soc.*, **39**, 7 (1965).
- (9) (a) R. P. Bell, J. P. Millington, and J. M. Pink, *Proc. R. Soc. London, Ser. A*, **303**, 1 (1968); (b) H. Dahn and J.-D. Aubort, *Helv. Chim. Acta*, **51**, 1348 (1968); (c) R. P. Bell and J. E. Critchlow, *Proc. R. Soc. London, Ser. A*, **325**, 35 (1971); (d) R. P. Bell and P. E. Sørensen, *J. Chem. Soc., Perkin Trans. 2*, 1740 (1972); (e) P. E. Sørensen, *Acta Chem. Scand., Ser. A*, **30**, 673 (1976); (f) U. L. Haldna, L. E.-J. Errelline, and H. J. Kuura, *Org. React. (USSR)*, **5**, 202 (1968).
- (10) J. E. Critchlow, *J. Chem. Soc., Faraday Trans. 1*, **68**, 1774 (1972).
- (11) R. P. Bell and P. G. Evans, *Proc. R. Soc. London, Ser. A*, **291**, 297 (1966).
- (12) R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).
- (13) R. P. Bell and E. C. Baughan, *J. Chem. Soc.* 1947 (1937); R. P. Bell and J. P. H. Hirst, *ibid.*, 1777 (1939).
- (14) (a) G. W. Meadows and B. de B. Darwent, *Trans. Faraday Soc.*, **48**, 1015

- (1952); (b) R. P. Bell and D. G. Horne, *J. Chem. Soc., Perkin Trans. 2*, 1371 (1972); (c) R. F. Atkinson and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 819 (1974); (d) V. Macháček and V. Štěrbá, *Org. React. (USSR)*, **13**, 328 (1976); (e) B. Capon, K. Nimmo, and G. L. Reid, *J. Chem. Soc., Chem. Commun.*, 871 (1976).
- (15) (a) P. Le Hénaff, *C. R. Acad. Sci.* **256**, 1752 (1963); (b) *ibid.*, **262**, 1667 (1966); (c) *ibid.*, **263**, 1205 (1966).
- (16) A. L. Mori, M. A. Porzio and L. L. Schaleger, *J. Am. Chem. Soc.*, **94**, 5034 (1972). Schaleger has argued that since the hydroxide ion catalyzed reaction presumably proceeds through the intermediate $^{-}OCR_2OR'$ all base-catalyzed reactions must proceed through the same intermediate and must represent general acid catalysis of the breakdown of the intermediate. However, the general-base catalyzed reaction may proceed by a different mechanism and it is likely that the addition and expulsion of alkoxide ion proceeds without buffer catalysis.
- (17) R. P. Bell and D. P. Onwood, *Trans. Faraday Soc.*, **58**, 1557 (1969).
- (18) (a) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 5637 (1973); (b) J. P. Fox and W. P. Jencks, *ibid.*, **96**, 1436 (1974).
- (19) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **81**, 1050 (1959); **82**, 795 (1960).
- (20) P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Am. Chem. Soc.*, **95**, 5960 (1973).
- (21) This value is based on calculated pK values for two carbonyl addition compounds which are in good agreement.¹⁸ However, the uncertainty in this value is as much as ± 1.5 units based on a statistically corrected value of $\Delta pK = 6.2$ units for the two dissociation constants of hexafluoroacetone hydrate (0.5 units of which was attributed to intramolecular hydrogen bonding (J. Hine and N. W. Flachskam, *J. Org. Chem.*, **42**, 1979 (1977)) and a value of 3.4 for the two amino groups in the addition compound of ethylenediamine and glyoxylic acid.²²
- (22) A. Hilton and D. L. Leussing, *J. Am. Chem. Soc.*, **93**, 6831 (1971), and personal communication, quoted in footnote 57 of ref 18b; a statistical correction of 0.6 units has been added to the measured pK of 4.81 for the diprotonated species.
- (23) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
- (24) M.-L. Ahrens and G. Maass, *Angew. Chem., Int. Ed. Engl.*, **7**, 818 (1968).
- (25) P. Valenta, *Collect. Czech. Chem. Commun.*, **25**, 853 (1960); H. G. Schecker and G. Schulz, *Z. Phys. Chem. (Frankfurt am Main)*, **65**, 221 (1969); H. C. Sutton and T. M. Downes, *J. Chem. Soc., Chem. Commun.*, 1 (1972).
- (26) Preliminary experiments carried out by E. Borcsok and B. Kosba in this laboratory have given values of $K_E = 33$ for ethanol and 4.9 for trifluoroethanol addition at 26 °C.
- (27) A. Levi, G. Modena, and G. Scorrano, *J. Am. Chem. Soc.*, **96**, 6585 (1974); R. A. McClelland and W. F. Reynolds, *Can. J. Chem.*, **54**, 718 (1976).
- (28) D. A. Jencks and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 7948 (1977).
- (29) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 4319 (1962).
- (30) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).
- (31) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 507 (1974).
- (32) (a) T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.*, **92**, 1681 (1970); B. Capon and K. Nimmo, *J. Chem. Soc., Perkin Trans. 2*, 1113 (1975).
- (33) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 464 (1977).
- (34) A. J. Kresge, personal communication.
- (35) B. Capon and R. B. Walker, *J. Chem. Soc., Perkin Trans. 2*, 1600 (1974).
- (36) R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970).
- (37) H. F. Gilbert and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 7931 (1977).
- (38) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 6970 (1977).
- (39) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, pp 198, 211-217.
- (40) J. M. Sayer, B. Pinsky, A. Schonbrunn, and W. Washtien, *J. Am. Chem. Soc.*, **96**, 7998 (1974).
- (41) A. Skrabel and H. H. Eger, *Z. Phys. Chem. (Leipzig)*, **122**, 349 (1926).
- (42) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **100**, 1228 (1978).
- (43) J. E. Reimann and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3973 (1966).
- (44) E. H. Cordes and H. G. Bull, *Chem. Rev.*, **74**, 581 (1974); B. M. Dunn and T. C. Bruice, *J. Am. Chem. Soc.*, **93**, 5725 (1971).
- (45) T. H. Fife, *Acc. Chem. Res.*, **5**, 264 (1972); E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).
- (46) W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 4731 (1972).
- (47) C. D. Ritchie, *J. Am. Chem. Soc.*, **97**, 1170 (1975).
- (48) R. P. Bell and P. E. Sørensen, *J. Chem. Soc., Perkin Trans. 2*, 1594 (1976).
- (49) D. J. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 451 (1977); J. M. Sayer and W. P. Jencks, *ibid.*, **99**, 464 (1977); D. J. Hupe and D. Wu, *ibid.*, **99**, 7653 (1977); D. J. Hupe, D. Wu, and P. Sheppard, *ibid.*, **99**, 7659 (1977).
- (50) J. Hine, *J. Am. Chem. Soc.*, **94**, 5766 (1972).
- (51) L. H. Funderburk and W. P. Jencks, *J. Am. Chem. Soc.*, in press.
- (52) The coordinates of the level lines are invariant upon transformation of the diagrams but, because of the changes in angles, the coordinates of a reaction coordinate that bisects the two level lines are different in the two diagrams.²⁸ This is evident in the present example, in which the "reaction coordinate" is rotated slightly clockwise from the line at which $\gamma' = \beta' = 0$ for the square diagram (Figure 6) and slightly counterclockwise from this line in the transformed diagram.
- (53) E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969); T. H. Fife and E. Anderson, *J. Org. Chem.*, **36**, 2357 (1971); B. M. Dunn, *Int. J. Chem. Kinet.*, **6**, 143 (1974).
- (54) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966).
- (55) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 1206 (1977).
- (56) E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 4377 (1968).
- (57) M. C. V. Sauer and J. O. Edwards, *J. Phys. Chem.*, **75**, 3004 (1971).
- (58) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 489 (1974).
- (59) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 8238 (1977).

Acidities and Basicities of Carboxylic Acids. Correlations between Core-Ionization Energies, Proton Affinities, and Gas-Phase Acidities

S. R. Smith and T. D. Thomas*

Contribution from the Department of Chemistry and Radiation Center,
Oregon State University, Corvallis, Oregon 97331. Received January 27, 1978

Abstract: Core-ionization energies for a number of carboxylic acids and esters have been measured with the view of establishing the relative importance of initial-state charge distribution and final-state charge rearrangement in determining core-ionization energies, proton affinities, and gas-phase acidities. Results are reported for $RCOOH$ ($R = H, CH_3, CF_3, CF_2H$), for $RCOOCH_3$ ($R = H, CH_3, CF_3$), for $RCOOC_2H_5$ ($R = H, CH_3, CF_3, CF_2H, CFH_2, CClH_2, CBrH_2$), and for acetone and methyl carbonate. A linear correlation with slope -1.6 is found between core-ionization energies and proton affinities for double-bonded oxygen. Compounds in which initial-state effects are important and those in which final-state effects are important fit the correlation line equally well. Although there is no simple correlation between anion proton affinity (the negative of acidity) and core-ionization energies, the data are consistent with an expected negative correlation when inductive effects are important and a positive correlation when relaxation is important. A quantitative analysis of these results is in good agreement with theoretical results obtained by Davis and Shirley. Correlations among the various core-ionization energies indicate that positive charge on a carboxyl group, whether produced by core ionization or by protonation, is extensively delocalized by valence-electron rearrangement.

One of the fundamental concepts in chemistry is that of acidity and basicity. In the most general terms acidity is the ability of a substance to accept negative charge and basicity is the ability to accept positive charge. In the Lewis definition,

the charge is transferred by gain or loss of an electron pair. In the Lowry-Brønsted definition, the charge is transferred by gain or loss of a proton.

Martin and Shirley,¹ noting the formal similarity between