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Nonenforced Concerted General-Acid Catalysis of the Dehydration Step in Formaldehyde Thiosemicarbazone Formation[1]

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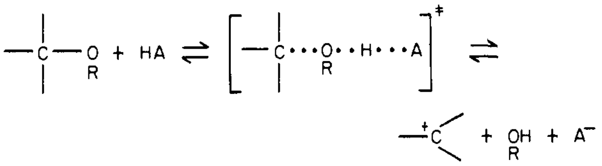
Abstract: At pH >6 the formation of formaldehyde thiosemicarbazone proceeds with rate-limiting dehydration of the carbinolamine intermediate, which is at equilibrium with formaldehyde hydrate and thiosemicarbazide ($K = 550\ M^{-1}$). At higher concentrations of formaldehyde a bis(formaldehyde) addition compound is formed, which undergoes dehydration more slowly. The dehydration step is subject to general-acid catalysis by phosphate and phosphonate buffers with $\alpha = 0.83$. A solvent deuterium isotope effect of $k_{HA}/k_{DA} = 2.6$ for catalysis by ethylphosphonate monoanion and published evidence support a concerted mechanism of catalysis. The calculated rate constant for formation of the O-protonated carbinolamine is $>10^4$ faster than the observed rate constant for dehydration and the rate constant for expulsion of water from this species is $<3 \times 10^7\ s^{-1}$. Thus, it appears that a concerted mechanism can exist when it is not enforced by the nonexistence of the O-protonated species. The secondary α-deuterium isotope effect of $k_H/k_D = 1.06$ ($1.03/D$) for catalysis by phosphate monoanion suggests an early transition state but other criteria suggest a central or late transition state for C–O cleavage.

Concerted general-acid–base catalysis through a class n mechanism provides a facile, widespread pathway for elimination–addition reactions of water and alcohols with both stable and unstable electrophilic carbon centers (eq 1).[2-9] A class n mechanism involves proton transfer to or from the nucleofugic-nucleophilic reactant.[9] There is evidence that, in at least some cases, the concerted mechanism is enforced because the intermediate species with a fully protonated leaving group (**1**) is so unstable that it has no significant lifetime, so that the reaction cannot proceed through a stepwise reaction mechanism.[5] We would like to know if the concerted mechanism is always enforced in this way or if the concerted mechanism can occur when the protonated intermediate has a significant lifetime.[10] The coexistence of stepwise and concerted mechanisms is common for the addition of hydroxide and alkoxide ions and appears as a positive deviation of the rate constant for the hydroxide ion reaction from the Brønsted plot for other base catalysts.[10,11] However, the coexistence of general- and specific-acid catalysis, which should be manifested as a positive deviation of the rate constant for catalysis by the proton from the Brønsted plot for general-acid catalysis, is rare.



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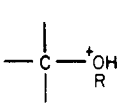

$$-\overset{|}{\underset{|}{C}}-\underset{R}{\overset{+}{O}H}$$

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It is convenient to describe elimination–addition reactions of this kind with three-dimensional reaction coordinate–energy contour diagrams in which the x and y axes represent coordinates for the proton transfer and C–O bonding processes.[10,12] It is possible to describe these reactions in such a way that horizontal and vertical cross sections through the diagram consist of no more than two energy wells and one energy maximum.[10] However, the coexistence of stepwise mechanisms that proceed through intermediates at the corners and a concerted mechanism that proceeds through the center of the diagram requires that there be three energy wells and two energy maxima along a diagonal cross section of the diagram. Although their theoretical significance is uncertain, we were curious to know whether such cross sections exist.

We report here the occurrence of general-acid catalysis of the dehydration step of formaldehyde thiosemicarbazone formation. This reaction was chosen because the stability of formaldehyde addition compounds and the small driving force for elimination from the weakly basic thiosemicarbazide group were expected to allow the formation of an O-protonated intermediate, **1**, with a significant lifetime.

Experimental Section

Materials. Dilute aqueous stock solutions of formaldehyde were prepared from commercial 37% formaldehyde after removal of formate by passage through a Dowex 1-hydroxide column. Formaldehyde concentration was determined by titration of hydroxide ion liberated upon addition of sodium sulfite.[13] Thiosemicarbazide was recrystallized from aqueous ethanol. Monobasic and dibasic potassium trichloromethylphosphonate, monobasic potassium chloromethylphosphonate and potassium ethylphosphonate were prepared by a published procedure.[11] Other chemicals were reagent grade. Glass-distilled water was used throughout.

Kinetics. Pseudo-first-order rate constants for thiosemicarbazone formation were determined spectrophotometrically at 262 nm in the

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[2] See, for example: Gravitz, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 507-515, and references 3-8.

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Table I. Equilibrium and Rate Constants for the Reactions of Thiosemicarbazide and Formaldehyde[a]

K_1, M^{-1}	550	K_4, M	0.14
K_3	30	k_3,[b] s^{-1}	2.4×10^{-3}
$K_1 + K_1K_3$, M^{-1}	1.7×10^4	k_{-3},[b] s^{-1}	8×10^{-5}
K_2, M^{-1}	210	k_4,[b] s^{-1}	1.3×10^{-4}

[a] Equilibrium and rate constants are defined in eq 2 and 6. They were determined as described in the text at 25 °C, ionic strength 1.0 M (KCl). [b] At pH 6.42, 0.1 M cacodylic acid.

presence of excess formaldehyde at 25 °C. The ionic strength was maintained at 1.0 M with potassium chloride. Rate constants were obtained from plots of ln $(A_\infty - A_t)$ against time. The final absorbance showed a slow decrease with time so that values of A_∞ were calculated by multiplying the maximum observed absorbance by $(1 - {}^1/_{2}{}^{n})^{-1}$, in which n is the number of half-times required to reach maximum absorbance; values of n were in the range 5–8. The plots were linear for ≥3 half-times except at the lowest concentrations of formaldehyde, in which the formaldehyde was not in large excess; rate constants for these experiments were estimated from the initial slopes of the plots. The reaction product has λ_{max} = 261 nm (λ_{max} for acetaldehyde thiosemicarbazone is 260 nm in water[14]); the secondary product that is formed after several hours (possibly an oxidation product) has λ_{max} = 254 nm. Buffer catalysis was examined at ≥4 buffer concentrations in the range 0.03–0.30 M. Experiments with trichloromethylphosphonate in the range pH 6.6–7.6 were carried out in the presence of a constant concentration of 0.1 M phosphate or ethylphosphonate buffer. Some catalysis by the basic species of the weaker acids was observed ($k_B \approx 0.05\ k_{HA}$ for ethylphosphonate dianion) but was not examined in detail.

The solvent deuterium isotope effect for catalysis by ethylphosphonate was determined from rate constants at six concentrations of buffer, 50% dianion, in the range 0.06–0.24 M in H_2O and D_2O. Secondary isotope effects were determined with formaldehyde and dideuterioformaldehyde prepared from the corresponding paraformaldehyde.[15] Three determinations were carried out, by using six, eight, and four different concentrations of phosphate buffer, 50% dianion, in the range 0.05–0.42 M. Formaldehyde and dideuterioformaldehyde concentrations were determined by titration with sodium sulfite[13] and from the change in absorbance at 262 nm of solutions containing initially 5×10^{-4} M thiosemicarbazide and $\sim 2 \times 10^{-5}$ M formaldehyde, on the basis of $\epsilon_{app} = 1.69 \times 10^4$ for the thiosemicarbazone, which gave identical results [ϵ is 3% larger than ϵ_{app} because 3% of the semicarbazone is hydrated (Table I)]. The kinetic measurements were carried out with 0.458 mM formaldehyde and 0.545 mM dideuterioformaldehyde and were analyzed as described elsewhere.[15]

Results

The pseudo-first-order rate constants for thiosemicarbazone formation in the presence of a large excess of formaldehyde at pH >6 show a nonlinear increase and an ordinate intercept as the formaldehyde concentration is increased up to 1 mM (Figure 1, lower line). This is the behavior that is expected for approach to equilibrium, with dehydration of the carbinolamine intermediate, C, as the rate-determining step (k_3, eq 2).[16] The leveling

$$\underset{F}{HOCH_2OH} + \underset{T}{RNH_2} \overset{K_1}{\rightleftharpoons} \underset{C}{RNHCH_2OH} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{P}{RN{=}CH_2} \quad (2)$$

of the rate at high concentrations of formaldehyde is caused by accumulation of the carbinolamine intermediate (K_1), and the intercept at zero formaldehyde concentration is the first-order rate constant for the rate-determining step of the reverse reaction, k_{-3} (eq 3).[17] The carbinolamine intermediate is actually formed by

$$k_{obsd} = k_F + k_R = \frac{k_3K_1[F]}{1 + K_1[F]} + k_{-3} \quad (3)$$

the addition of thiosemicarbazide to free formaldehyde, but the concentration of free formaldehyde is negligible in aqueous solution. The observation of first-order kinetics with respect to thiosemicarbazide shows that the dehydration of formaldehyde hydrate is not rate limiting under the conditions of these experiments, so that it is convenient to express the formaldehyde concentration as the total concentration of formaldehyde.

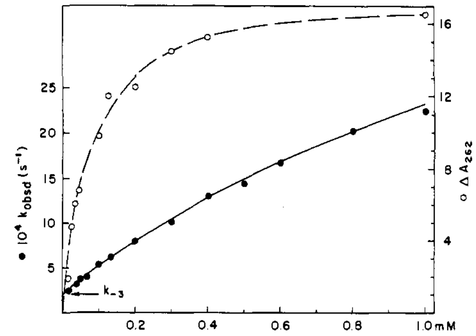

Figure 1. The rate and extent of thiosemicarbazone formation at low concentrations of formaldehyde. Lower curve: pseudo-first-order rate constant for thiosemicarbazone formation in 0.1 M cacodylate buffer, pH 5.89, 25 °C, ionic strength 1.0 M (KCl). The solid line is drawn based on eq 3 and the equilibrium constants in Table I. Upper curve: the observed change in absorbance at equilibrium expressed as ΔA_{262}/[mM thiosemicarbazide]/cm. The dashed line is drawn on the basis of an equilibrium constant of 1.7×10^4 M^{-1} (Table I) and ϵ = 17 600 for formaldehyde thiosemicarbazone.

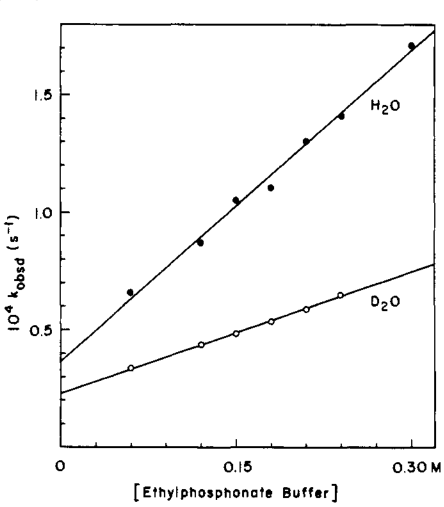

Figure 2. Catalysis by ethylphosphonate buffers, 50% dianion, of thiosemicarbazone formation in the presence of 0.5 mM formaldehyde in H_2O and D_2O, ionic strength 1.0 M (KCl), 25 °C.

The equilibrium and rate constants for the reaction were obtained from a plot of $1/(k_{obsd} - k_{-3})$ against $1/[F]$ according to eq 4 and are summarized in Table I. The solid line in Figure 1, which is calculated from these constants and eq 3, provides a satisfactory fit to the results.

$$\frac{1}{k_{obsd} - k_{-3}} = \frac{1}{K_1k_3[F]} + \frac{1}{k_3} \quad (4)$$

The increase in the absorbance of thiosemicarbazone at 262 nm with increasing formaldehyde concentration at equilibrium is described by an equilibrium constant, K_{obsd}, that is equal to $K_1(1 + K_3)$.[18] The data fit a value of $K_{obsd} = 1.7 \times 10^4$ M^{-1} (Figure 1, upper line), which is identical with the equilibrium constant obtained from the kinetic measurements (Table I).

Catalysis of the reaction by ethylphosphonate buffers in H_2O and D_2O is shown in Figure 2. The observed rate constants are related to the rate constants for the dehydration step, k_3, by eq 5, which is obtained by substituting the dehydration equilibrium

$$k_{obsd} = k_3[K_1[F](1 + K_1[F])^{-1} + K_3^{-1}] \quad (5)$$

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(18) The ratio [P]/[C] = K_3 is independent of [F] so that the observed change in absorbance at equilibrium (Figure 1) depends on the equilibrium constant K_{obsd} = [C + P]/[T][F] = $K_1(1 + K_3)$.

Table II. General Acid Catalysis of the Dehydration Step of Formaldehyde Thiosemicarbazone Formation

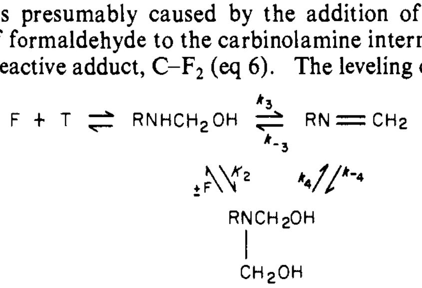
catalyst	pK_a[a]	fraction acid	k_{cat},[b] $M^{-1}\,s^{-1}$	k_{HA},[c] $M^{-1}\,s^{-1}$
ethylphosphonate	7.6	0.50	1.77×10^{-3}	3.34×10^{-3}
		0.29	1.11×10^{-3}	
phosphate	6.46	0.40	6.8×10^{-3}	1.62×10^{-2}
		0.20	3.72×10^{-3}	
chloromethylphosphonate	5.94	0.30	1.26×10^{-2}	3.68×10^{-2}
		0.10	5.6×10^{-3}	
trichloromethylphosphonate	4.24	5.8×10^{-3}	8.5×10^{-3}	1.38
		5.5×10^{-4}	1.41×10^{-3}	
		3.5×10^{-4}	7.6×10^{-4}	

[a] By titration and ref 4. [b] Second-order rate constant for buffer-catalyzed dehydration of the carbinolamine intermediate, calculated from eq 5. The rate constants were measured with 5×10^{-4} M formaldehyde and 3×10^{-5} M thiosemicarbazide at 25 °C, 1.0 M ionic strength (KCl). [c] Rate constants for catalysis of the dehydration step by acids.

constant, $K_3 = k_3/k_{-3}$, into eq 3. At 0.5 mM formaldehyde concentration this reduces to $k_3 = 4.03k_{obsd}$. Plots of k_3 against total buffer concentration gave k_{cat} as the slope and k_0 as the intercept. A plot of k_0 against 10^{-pH} gave a value of $k_{H^+} = 4.8 \times 10^3\ M^{-1}\,s^{-1}$ for the proton-catalyzed reaction and a small intercept which, if significant, could represent a "water" reaction with $k \approx 3 \times 10^{-5}\ s^{-1}$ or catalysis by hydroxide ion. Plots of k_{cat} against the fraction of the acidic form of the buffer gave catalytic constants, k_{HA}, for general-acid catalysis of the dehydration step by a series of buffer acids (Table II). The solvent deuterium isotope effect for catalysis by ethylphosphonate buffers is $k_{HA}/k_{DA} = 2.6$ under conditions in which >90% of the catalysis is by $EtPO_3H^-$. A Brønsted plot of the catalytic constants gives a slope of $\alpha = 0.83$ for catalysis by phosphate and substituted-phosphonate monoanions, with a negative deviation for catalysis by the solvated proton (Figure 3). Also shown in Figure 3 is a Brønsted plot for catalysis of the reaction in the presence of 5 mM formaldehyde, which gives a value of $\alpha = 0.82$.

The secondary α-deuterium isotope effect for thiosemicarbazone formation catalyzed by phosphate buffer (1:1 monoanion–dianion) was found to be 1.14 ± 0.053, 1.04 ± 0.048, and 1.04 ± 0.032 in three separate experiments for $k(HOCH_2OH)/k(HOCD_2OH)$. These gave a weighted average of $k_H/k_D = 1.03 \pm 0.02$ (per deuteron). The intercepts at zero buffer concentration, which represent primarily the proton-catalyzed reaction, gave isotope effects of 0.99 ± 0.031, 1.05 ± 0.034, and 1.01 ± 0.04 for k_{obsd} and a weighted average of $k_H/k_D = 1.01 \pm 0.01$ (per deuteron).

At concentrations of formaldehyde above 1 mM the reaction rate decreases and no longer follows eq 3 (Figure 4). This inhibition is presumably caused by the addition of a second molecule of formaldehyde to the carbinolamine intermediate to give a less reactive adduct, C–F_2 (eq 6). The leveling of the rate



$$\begin{array}{ccccc} F + T & \rightleftharpoons & \mathrm{RNHCH_2OH} & \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} & \mathrm{RN{=}CH_2} \\ & & \pm F \searrow\!\nwarrow K_2 & & k_4 \nearrow\!\swarrow k_{-4} \\ & & & \mathrm{RNCH_2OH} & \\ & & & | & \\ & & & \mathrm{CH_2OH} & \\ & & & \mathrm{C{-}F_2} & \end{array} \tag{6}$$

at high formaldehyde concentration (Figure 4) shows that the addition compound C–F_2 can also undergo dehydration, with the rate constant k_4; the limiting rate constant at infinite formaldehyde concentration is larger than k_{-3}. There is also a decrease in the equilibrium concentration of semicarbazone with increasing formaldehyde concentration in the range 0.02–0.33 M (not shown), which is half-maximal at 0.14 M formaldehyde. The minimal mechanism in eq 6 is consistent with the observed inhibition, but insufficient data are available to evaluate completely all of the rate and equilibrium constants for the reaction at high formaldehyde concentrations. The decrease in the equilibrium concentration of thiosemicarbazone gives a value of $K_{app} = (1 + 1/K_3)K_4 = 0.14$ M, from which values of $K_4 = 0.14$ M and $K_2 = 210\ M^{-1}$ were calculated from the known value of K_3 (Table I) and the relation $K_2 = K_3/K_4$. This value of K_2 accounts for the inhibition of the rate of semicarbazone formation and a kinetic treatment of eq 6[19] gives $k_4 = 1.3 \times 10^{-4}\ s^{-1}$ in 0.1 M cacodylate buffer, pH 6.4 (6% of the value of k_3 under these conditions), which gives a fair fit to the observed rate constants (solid line, Figure 4); however, the relative contributions of proton and buffer catalyses and the uncatalyzed reaction to the observed rate constants were not determined. The fact that the Brønsted plot for catalysis of thiosemicarbazone formation in the presence of 5 mM formaldehyde has the same slope as that for the dehydration rate constant k_{HA} (Figure 3) suggests that the inhibition is relatively constant as the pH and buffer concentration are changed.

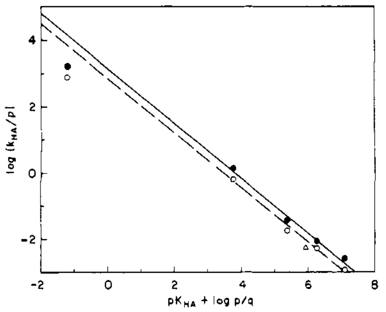


Figure 3. Brønsted plots for general-acid catalysis of carbinolamine dehydration. Upper line: values of k_{HA} obtained with 0.5 mM formaldehyde. Lower line: observed second-order rate constants for general-acid catalysis of thiosemicarbazone formation with 5.0 mM formaldehyde. Triangle: catalysis by cacodylic acid.

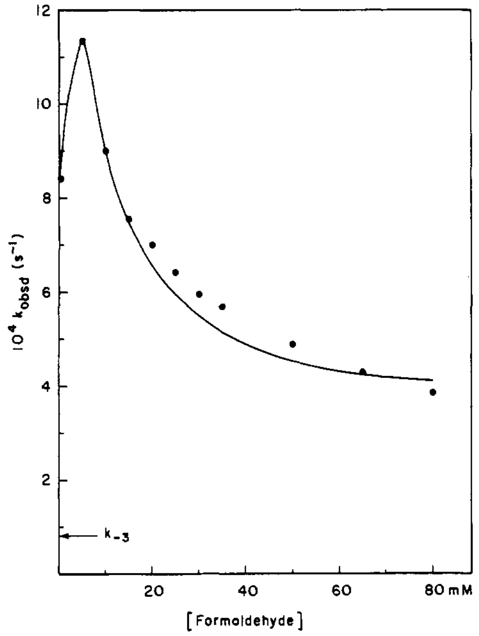


Figure 4. Inhibition of the rate of thiosemicarbazone formation at high concentrations of formaldehyde. The pseudo-first-order rate constants were obtained in 0.1 M cacodylate buffer, pH 6.42, ionic strength 1.0 M (KCl), 25 °C. The solid line is drawn by using the rate and equilibrium constants in Table I and the kinetic equation in ref 19.

The pK_a of the O-protonated carbinolamine intermediate, $RNHCH_2OH_2^+$, was estimated to be −3.6 from the pK_a of −1.98 for $MeOH_2^+$, $\sigma_1 = 0.19$ for thiosemicarbazide, $\rho_1 = 8.4$ for the ionization of alcohols, and the assumption that the value of ρ_1 for acid dissociation is independent of the absolute charge on the molecule.[20-22] The value of $\sigma_1 = 0.19$ was estimated from values

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(19) The kinetic solution to eq 6 is $k_{obsd} = k_3(1/((K_1[F])^{-1} + K_2[F] + 1) + K_3^{-1}) + k_4(K_1K_2[F]^2/(1 + K_1[F] + K_1K_2[F]^2) + K_2[F]/K_3)$, an equation with only one unknown, k_4.

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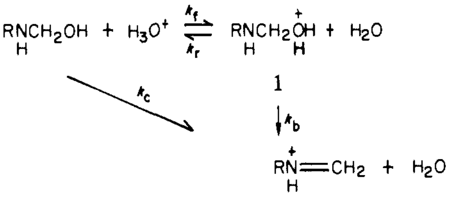
of σ_I = 0.15, 0.26, and 0.21 for NH_2NH-, CH_3CONH-, and $H_2NCONH-$, respectively.[23]

Discussion

The leveling of the pseudo-first-order rate constants with increasing formaldehyde concentration (Figure 1) is caused by accumulation of the carbinolamine intermediate and confirms that the observed general-acid catalysis near neutral pH represents catalysis of the dehydration step of thiosemicarbazone formation (k_3, eq 2).[16] At formaldehyde concentrations higher than 1 mM the rate decreases because of a slower dehydration rate of the bis(formaldehyde) addition compound (Figure 4). As the formaldehyde concentration is increased further, the rate levels off, suggesting that the bis(formaldehyde) carbinolamine also undergoes dehydration, but more slowly than the monohydroxymethyl adduct (k_4, eq 6).

Specific-acid catalysis of the dehydration of the carbinolamine intermediate, if it occurs, proceeds through an equilibrium protonation step with the equilibrium constant $K = k_f/k_r$, followed by rate-limiting dehydration with the rate constant k_b (eq 7). The



$$\underset{\text{H}}{\text{RNCH}_2\text{OH}} + H_3O^+ \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \underset{\text{H}\quad\text{H}}{\text{RNCH}_2\overset{+}{\text{O}}\text{H}} + H_2O \xrightarrow{k_b} \underset{\text{H}}{\text{R}\overset{+}{\text{N}}}\text{=CH}_2 + H_2O \qquad (7)$$

rate constant for protonation, k_f, may be calculated from the equilibrium constant, $K = 10^{-3.6} \times 55.5 = 1.3 \times 10^{-2}$ (the estimated pK_a of the O-protonated carbinolamine is −3.6, as described in the Results), and the rate constant for the thermodynamically favorable proton transfer, k_r, which should be at least as large as the rate constant of 1.1×10^{10} M^{-1} s^{-1} for the thermoneutral transfer of a proton between water molecules.[24] The calculated value of $k_f = >1.3 \times 10^8$ M^{-1} s^{-1} is 2.8×10^4 larger than the observed rate constant for catalysis of the dehydration step by the proton, 4.8×10^3 M^{-1} s^{-1}. This shows that the O-protonated carbinolamine is formed rapidly, at equilibrium, compared with the observed dehydration step.[25]

An upper limit for the rate constant k_b, for cleavage of the O-protonated carbinolamine, can be calculated from K and the observed rate constant k_{H^+}. If specific-acid catalysis were significant, the observed rate constant for specific-acid catalysis would be equal to k_bK. If all of the proton-catalyzed reaction represented specific-acid catalysis, the value of k_b would be given by $k_b = 55.5 \cdot k_{H^+}/K = 1.9 \times 10^7$ s^{-1}. However, the rate constant for catalysis by the proton falls below the Brønsted line for general-acid catalysis of the reaction by buffer acids (Figure 3).[26] Therefore, much or all of the proton-catalyzed reaction can be accounted for by general-acid catalysis, there is no indication of an additional specific-acid-catalyzed reaction (which would cause a positive deviation from the Brønsted line), and the value of k_b for the cleavage of **1** is $<1.9 \times 10^7$ s^{-1}. Thus, the O-protonated carbinolamine exists as a relatively stable species under the conditions of these experiments.

The conclusion that the O-protonated carbinolamine exists rests on the assumption that protonated weak bases exist in dilute aqueous solution. If there is no barrier for the transfer of a proton from such a species to water, it cannot be said to exist. The facts that dissociation constants for protonated alcohols and ethers can be measured by various spectrophotometric techniques and that the amount of protonation is described by acidity functions that are well behaved over a range of acidity extending into dilute acid solutions suggest that these species do exist.[22,27] The strongest evidence that protonated weak bases have a meaningful existence is probably the demonstration that protonation of aliphatic primary amides on nitrogen, to form an acid with a pK_a close to −8,[28] gives a species with a lifetime long enough to allow isomerization of the amide E and Z protons by rotation around the C–N bond at a rate that is slightly faster than the rate of deprotonation.[29] Although the rate constant for rotation about the $C-NH_3^+$ bond of an N-protonated amide is not known, the rate constant for rotation of the methyl group of ethyl bromide is 7×10^{11} s^{-1} and the barrier for rotation is smaller when the methyl group is adjacent to sp^2 carbon (2.8 kcal mol^{-1} for ethyl bromide and 0.5 kcal mol^{-1} for acetic acid).[30] The rate of rotation may be slowed by hydrogen bonding to solvent molecules. Finally, the fact that proton transfers are usually not diffusion controlled when the proton transfer is not strongly favorable thermodynamically[31] suggests that a significant Gibbs energy barrier exists for the transfer of a proton from an O-protonated carbinolamine to water, for which ΔpK is only ~2.

There is strong evidence that general-acid–base catalysis of the expulsion and addition of alcohols and water proceeds through a concerted, one-step, class n reaction mechanism (eq 1). The observed structure-reactivity behavior further suggests that there is significant interaction, or coupling, between the proton transfer and changes in C–O bonding in the transition state.

(1) Brønsted α values range from <0.5 to approaching 1.0 and show a continuous, linear increase with increasing pK of the leaving alcohol that can be described by a positive interaction coefficient $p_{xy'} = \partial\beta_{1g}/-\partial pK_{HA} = \partial\alpha/\partial pK_{1g}$.[32] This result has been obtained for a large number of reactions[2] including the expulsion of ROH in benzaldehyde tosylhydrazone formation.[4] It is inconsistent with a hydrogen-bonding mechanism involving a double potential well for the proton in the transition state. In such a mechanism the proton would be expected to rest in one or the other well and to give a value of α near 0.2 or 0.8; a large change in the position of the proton would give a sudden change between a small and a large value of α as the proton moved from one well to the other, rather than the observed linear increase in α. This result is consistent with a coupled, concerted mechanism or a hydrogen-bonding mechanism with a single well for the proton.[5,33] All of

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(25) Similar values of the rate constant for carbinolamine protonation, k_f, are obtained by two alternative methods. If protonation follows an Eigen curve with a limiting rate constant of 4×10^{10} M^{-1} s^{-1} (Bell, R. P. "The Proton in Chemistry", 2nd ed.; Cornell: Ithaca, N.Y., 1973; p 127) and a change in rate-determining step at $\Delta pK = 0$, the rate constant for the thermodynamically unfavorable proton transfer to the carbinolamine is $k_f = 5 \times 10^8$ M^{-1} s^{-1}. An upper limit for k_f can be calculated by assuming that the rate constant for the thermodynamically favorable proton transfer in the reverse direction is the same as for the recombination of the proton and hydroxide ions in water, $k_r = 1.4 \times 10^{11}$ M^{-1} s^{-1} (Eigen, M.; de Maeyer, L. *Naturwissenschaften* **1955**, *42*, 413–414), which gives $k_f = 1.8 \times 10^9$ M^{-1} s^{-1}. The rate constant for protonation by trichloromethylphosphonate monoanion is $k_f = 1.5 \times 10^2$ M^{-1} s^{-1}, based on $k_r = 10^{10}$ M^{-1} s^{-1} for protonation of trichloromethylphosphonate dianion by the O-protonated carbinolamine (Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19) and $\log (k_f/k_r) = -(4.24 + 3.6)$. This rate constant is 100 times larger than $k_{HA} = 1.38$ M^{-1} s^{-1} for general-acid catalysis of carbinolamine cleavage by trichloromethylphosphonate monoanion.

(26) Part or all of the negative deviation of the proton from the Brønsted plot for catalysis by phosphonates can be accounted for by an electrostatic effect (Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* **1973**, *95*, 803–806. Chwang, W. K.; Eliason, R.; Kresge, A. J. *Ibid.* **1977**, *99*, 805–808. The proton fits on the Brønsted line for catalysis by carboxylic and cacodylic acids.[4]).

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these carbinolamine dehydrations have similar properties and the value of $\alpha = 0.83$ for formaldehyde thiosemicarbazone formation is close to the value of $\alpha = 0.80$ for benzaldehyde semicarbazone formation catalyzed by a series of phosphonate buffers.[11]

(2) The dependence of log k on the pK of the leaving group, β_{lg}, is characteristically close to zero for catalysis by acetic acid and changes to positive and negative signs with changing pK of the acid, according to a positive $p_{xy'}$ coefficient.[2] A value of $\beta_{\mathrm{lg}} \approx 0$ means that there is little change in the charge on the leaving oxygen atom between the reactants and the transition state. This result is difficult to explain unless there is a cancellation of the positive charge development resulting from proton transfer ($\alpha = 0.83$ for formaldehyde thiosemicarbazone formation) and the negative charge development resulting from C–O bond cleavage. The linear change in the "effective charge" on the leaving oxygen atom, as measured by β_{lg}, with changing pK_{a} of the acid can be as large as 0.5, including both positive and negative values.[4,11] This result is particularly difficult to account for by a stepwise mechanism. When the value of α is large, any hydrogen-bonding mechanism must involve hydrogen bonding of the conjugate base of the catalyst to the O-protonated carbinolamine (**1**). The expulsion of an O-protonated alcohol to give an uncharged alcohol will proceed through a transition state in which there is a partial positive charge on the leaving oxygen atom. This is inconsistent with the negative values of β_{lg} for weak acids and weakly basic leaving groups, which show that there is a net development of negative charge on the leaving oxygen atom in the transition state. The negative values of β_{lg} also make it unlikely that the O-protonated carbinolamine is on the reaction path for the concerted mechanism.

(3) Although α increases with increasing basicity of the leaving group, it shows no change or decreases with increasing acidity of the acid (cf. the negative deviation for $k_{\mathrm{H^+}}$ in Figure 3). This corresponds to a coefficient $p_x = \partial\alpha/\partial \mathrm{p}K_{\mathrm{HA}} \geq 0$ and is the expected behavior for a concerted mechanism with participation of the proton-transfer process in the transition state. A hydrogen-bonded proton in a potential well would be expected to shift its position toward the stronger base with changes in the pK of either the acid or the base so that α should show comparable increases with increasing strength of the base and of the acid.[11]

(4) Plots of log k against the pK of the leaving alcohol are characteristically concave upward, corresponding to a large negative coefficient $p_{y'} = \partial\beta_{\mathrm{lg}}/-\partial \mathrm{p}K_{\mathrm{lg}}$.[5,7] This corresponds to movement of the transition state toward a cationic structure as that structure becomes more stable (an anti-Hammond, "perpendicular" effect[34]). Such a shift is expected for a concerted reaction involving both proton transfer and C–O cleavage but is expected to be small or absent if there is only C–O cleavage in the transition state. This corresponds to the behavior that is expected for a diagonal reaction coordinate on a reaction coordinate–energy diagram in which the axes are defined by the observed structure-reactivity coefficients.[15,32] The opposite behavior is observed for carbamate cleavage, which is believed to proceed through a hydrogen-bonding mechanism.[35]

(5) The acid-catalyzed hydrolysis of substituted benzaldehyde acetals and the cleavage of Meisenheimer complexes show small increases in ρ with increasing strength of the catalyzing acid and increases in α with electron-withdrawing substituents on the ring that correspond to a positive coefficient $p_{xy} = \partial\rho/-\partial \mathrm{p}K_{\mathrm{HA}} = \partial\alpha/\partial\sigma$.[3,6,7] This is also the expected behavior for a concerted mechanism with a diagonal reaction coordinate on an energy contour diagram and would not be expected for a vertical reaction coordinate with only C–O cleavage in the transition state.[32] However, no p_{xy} coefficient could be detected for the dehydration step of benzaldehyde semicarbazone formation.[11] This was interpreted as evidence for an overall contraction of the transition state with increasing acid strength, which could explain the large difference between the $p_{xy'}$ and p_{xy} effects.

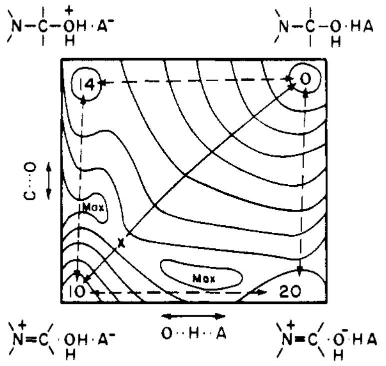

Figure 5. Reaction coordinate diagram to show how concerted (diagonal) and stepwise pathways through metastable intermediates (dashed lines) could coexist. The diagram is drawn for an acid catalyst of pK = 7 at pH 7, and the Gibbs energies of the intermediates are indicated. The contour lines are drawn at 3-kcal intervals. The energy of the saddle point on the left side (specific-acid catalysis) is a lower limit, and the height of the barrier on the right side is uncertain. No corrections were made for the equilibrium constants for formation of encounter complexes, which may be stabilized by hydrogen bonding.

(6) In some reactions of this class a stepwise mechanism is not possible because the "intermediate" in such a mechanism is formed too slowly and, if formed, would have too short a lifetime to exist, so that the mechanism must be concerted. For example, O-protonation of $\mathrm{CF_3CH_2OCH_2O^-}$ to form the dipolar intermediate that is required for a stepwise mechanism is 10^5 slower than is required to account for the observed rate of cleavage of the hemiacetal and the lifetime of a hydrogen-bonded "intermediate" would have to be less than 10^{-14} s.[5]

(7) The deuterium isotope effect of $k_{\mathrm{HA}}/k_{\mathrm{DA}} = 2.6$ for formaldehyde thiosemicarbazone formation supports a concerted mechanism with significant loss of zero-point energy of the proton undergoing transfer in the transition state. Isotope effects of this magnitude can result from strong, symmetrical hydrogen bonds with a small or negligible barrier for transfer of the proton between two potential wells,[36] but with $\alpha = 0.83$ a hydrogen-bonded proton would be expected to remain in a single well and exhibit only a small isotope effect.

We conclude that concerted general-acid catalysis can occur when it is not required to occur by the nonexistence of the "intermediate" for a stepwise reaction. Concerted catalysis provides a low-energy reaction path that serves to avoid the formation of the thermodynamically unstable intermediate, **1**, and the slightly unfavorable transition state for its breakdown to products. This conclusion can be illustrated by the reaction coordinate energy contour diagram of Figure 5 for general-acid catalysis by an acid of pK = 7.[10,12] The reaction proceeds through the transition state *x* of a concerted reaction mechanism, which has a large amount of proton transfer and moves in a characteristic manner on the reaction surface as the substituents on the reactants and catalyst are changed.[10,32] The O-protonated carbinolamine intermediate in the upper left corner exists in a potential well, because there are significant barriers for both C–O cleavage and proton transfer.[37] The pathway through this intermediate corresponds to specific-acid catalysis, which is too slow to be observed. The uncatalyzed expulsion of $\mathrm{HO^-}$, which corresponds to the uncatalyzed addition of $\mathrm{HO^-}$ or $\mathrm{RO^-}$ or to specific-base catalysis in the reverse direction (eq 8), proceeds through the lower right

$$\mathrm{RNHCH_2OR} \rightleftharpoons \mathrm{RNH^+{=}CH_2} + {}^-\mathrm{OR} \qquad (8)$$

corner of the diagram. The rate constant for this reaction path characteristically falls above the Brønsted line for general-acid–base catalysis. If the small intercept in the plot of k_0 against $10^{-\mathrm{p}H}$ represents a "water" reaction in formaldehyde thiosemicarbazone

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[34] Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915–2927.

[35] Ewing, S. P.; Lockshon, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 3072–3084.

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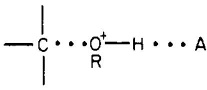
[37] The reasons for believing that there is a barrier for proton transfer to water in the proton-catalyzed reaction have been described above; it is not certain that there is a barrier for proton transfer to stronger bases.

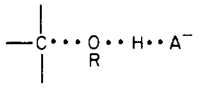
formation, the second-order rate constant for this step of $(7 \times 10^{-5}/55.5)$ M^{-1} s^{-1} is 10^3 larger than predicted by the Brønsted plot for concerted general-acid catalysis. Smaller positive deviations from the Brønsted plots for the "water" reaction are observed in other hydrazone-forming dehydrations for which more accurate values of this rate constant are available[38] and there is no doubt that there is a barrier for attack of the oxyanion in many reactions of this class such as the attack of HO^- or RO^- on aldehydes, esters, imidates, and phthalimidium ion.[2,5,39]

Thus, we conclude that it is possible for three potential wells to exist along the diagonal cross section from the upper left to the lower right corner of the diagram. This means that this class of reaction can proceed concurrently through the three pathways shown in Figure 5 and the transition states **2**–**4**. Transition state



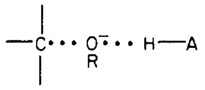
$$-\overset{|}{\underset{|}{C}}\cdots\underset{R}{\overset{+}{O}}-H\cdots A^-$$

2



$$-\overset{|}{\underset{|}{C}}\cdots\underset{R}{O}\cdots H\cdots A^-$$

3



$$-\overset{|}{\underset{|}{C}}\cdots\underset{R}{O^{\bar{\delta}}}\cdots H-A$$

4

2 ($A^- = H_2O$) is too unstable to contribute significantly to formaldehyde semicarbazone formation, but must exist. Pathways in which the fully protonated or deprotonated alcohol is stabilized by hydrogen bonding to a buffer base or acid (A^- or HA) should also exist.[35,40]

Why is it that coexistence of the concerted general-acid–base catalyzed pathway through the center of the diagram and the stepwise pathway of specific-base-catalyzed addition through the lower right corner is observed frequently, whereas coexistence of the concerted and stepwise pathways for acid-catalyzed breakdown (through the center and the upper left corner, respectively) is rare or unknown for this group of reactions? Specific-acid catalysis must occur whenever the protonated intermediate has a significant lifetime, but it is too slow to contribute significantly to the observed rate of formaldehyde thiosemicarbazone formation.

Specific-base or -acid catalysis must exist and contribute to the observed rate whenever a stable intermediate exists with a pK_a *in the range -1.7 to +15.7* (this generalization may not apply to certain reactions in which proton transfer is slow such as proton removal from carbon in elimination reactions). Hydroxide ion must catalyze the addition of water or trifluoroethanol by specific base catalysis, for example, because concerted acid–base catalysis requires that proton transfer between the catalyst and the initial reactant be thermodynamically unfavorable.[41] If proton transfer is thermodynamically favorable, it will occur rapidly and the reaction will proceed through a mechanism of specific-base or -acid catalysis. Similarly, the expulsion of amines from addition compounds usually occurs by specific-acid catalysis because proton transfer from H_3O^+ to the amine is thermodynamically favorable. Concerted general-acid catalysis of formaldehyde thiosemicarbazone formation is possible because the p*K* of the O-protonated intermediate is 1.9 units below that of H_3O^+. However, this small ΔpK means that concerted catalysis is only barely permitted, as is also the case for catalysis by weak acids of the expulsion of nitrophenols from acetals,[3,9] so that it is likely that examples will be found in which general- and specific-acid catalysis can be observed concurrently. The specific-acid catalysis should appear as a positive deviation of the rate constant for H_3O^+ above the Brønsted line for concerted catalysis and should show a large inverse solvent deuterium isotope effect. The positive deviation means that general-acid catalysis will only be detectable with weak buffer acids. In fact, the reversible addition of water to triarylcarbonium ions provides a likely example of this situation.[42]

Thus, we can identify four situations in which specific-acid catalysis of class n reactions can occur:

(1) It *must* occur when the pK_a of the protonated leaving group is >−1.7, proton transfer is fast, and the intermediate exists, because concerted catalysis by the proton is then forbidden.[41]

(2) It will probably occur when the protonated intermediate exists and α for general-acid catalysis increases to 1.0 because of increasing instability of the unsaturated product or changing p*K* of the leaving group, according to the relationships $p_{xy} = \partial\alpha/\partial\sigma$ and $p_{xy'} = \partial\alpha/\partial pK_{lg}$, respectively.[7,10,32,43] It may merge with catalysis by hydrogen bonding to the protonated leaving group, as in the cleavage of carbamates and sulfite addition compounds.[35,40]

(3) It will occur when the rate-limiting step is diffusion-controlled separation of the protonated leaving group from the unsaturated product or intermediate, as in acetal hydrolysis, because the proton is completely transferred in the rate-limiting transition state.[7,9] This mechanism will hold over only a limited range, because it will become a preassociation mechanism as the intermediate becomes less stable.[44,45]

(4) It will occur in a preassociation mechanism when attack of the incoming nucleophile is rate determining and the leaving alcohol is a "spectator".[46] This will also hold for only a limited range with alcohol leaving groups in aqueous solution, because only a few alcohols are more nucleophilic than water so that attack of water can be rate determining (in the hydrolysis of a phenyl acetal, for example, water would attack an intermediate oxocarbonium ion faster than phenol, so that phenol expulsion would be rate determining).

Imbalance. There are discrepancies in the amount of C–O cleavage in the transition state of this reaction as measured by different parameters, which suggest that there is an imbalance between the extent to which the different processes measured by these parameters have taken place in the transition state. Similar imbalances have been noted in a number of other reactions.[47] (1) The secondary α-deuterium isotope effect for formaldehyde semicarbazone formation is only $k_H/k_D = 1.06$ (1.03 per deuterium) for catalysis by phosphate monoanion and 1.01 (per deuterium) for catalysis by the proton. These values may be compared with $k_H/k_D = 1.63$ $(1.28/D)$ for the uncatalyzed cleavage of formaldehyde hemiacetal anions[15] and $K_D/K_H = 1.37 \pm 0.02$ for the equilibrium addition of water or amines to acetaldehyde, pentanal and benzaldehyde.[48-50] This suggests an early transition state for the former reaction, with little change from the sp^3 hybridization of the reactants. Very similar results and conclusions have been reported previously for the proton-catalyzed dehydration step of benzaldehyde semicarbazone and phenylhydrazone formation;[49] in the reverse direction, the secondary isotope effects suggest late, sp^3-like transition states for the addition of water to a protonated benzaldehyde imine[51] and for catalysis by acetate buffer of pentanal hydration.[50] (2) The dehydration

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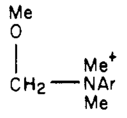
step of benzaldehyde semicarbazone formation follows ρ_n, not ρ, indicating that there is little or no electron donation by resonance or rehybridization in the transition state, although there is a large amount of resonance stabilization in the protonated imine product.[11] (3) An early transition state is suggested by the value of β_N for the acid-catalyzed dehydration step in the formation of a series of benzaldehyde hydrazones of only 0.4, some of which is simply electrostatic stabilization of the proton in the transition state.[38] However, other parameters indicate a large amount of C–O bond cleavage in the transition state: (1) The Brønsted α values for expulsion of water and alcohols are generally large, indicating a large amount of proton transfer, but the values of β_{lg} are small and sometimes negative.[4,11] This suggests that positive charge development on the leaving oxygen atom from proton transfer is compensated by a comparable or larger amount of C–O bond cleavage. (2) The ρ value of -1.9 for acid catalysis of the dehydration step of benzaldehyde semicarbazone formation is 90% of the value of $\rho = -2.1$ for product formation, suggesting a large amount of C–O bond cleavage in the transition state.[11]

A small fraction of the difference in the secondary α-deuterium kinetic isotope effects of $k_H/k_D = 1.03/D$ for phosphate-catalyzed formaldehyde semicarbazone formation and the values of 1.28–1.39 for hemiacetal cleavage and equilibrium loss of water can be accounted for by an electrostatic effect that reflects the apparent electron-donating effect of deuterium compared with protium.[52] On the basis of the value of $K_D/K_H = 1.05/D$ for the protonation of methylamine[53] and with the assumption of the development of a full positive charge adjacent to the formaldehyde carbon atom in the transition state, the corrected isotope effect is $k_H/k_D = 1.05 \times 1.03 = 1.08$. The hypothesis that the imbalance results from partial bond formation at the central carbon atom by a second water molecule in the transition state is improbable, because such bond formation would be expected to hinder the reverse, hydration reaction.

A similar imbalance between secondary isotope effects and other parameters is found for the reactions of amines and oxyanion nucleophiles with the formaldehyde carbon atom of *N*-methoxymethyl-*N,N*-dimethylanilinium ions, **5**, which exhibit $k_H/k_D =$



$$\mathrm{MeO{-}CH_2{-}\overset{+}{N}(Me)_2Ar}$$

5

$(1.07–1.08)/D$.[45] A number of criteria indicate that these reactions proceed through a carbonium ion-like transition state with little bond formation to the nucleophile, including the small values of $\beta_{nuc} = 0.14$ and a Swain–Scott n value of 0.3. Large, polarizable nucleophiles such as I^- and RS^- give large isotope effects of $k_H/k_D = (1.14–1.18)/D$. These results suggest that with small, "hard" nucleophiles and leaving groups, secondary α-deuterium isotope effects indicate more sp^3 character in the transition state than do other measures of transition-state structure. It appears that rehybridization or changes in the restriction to vibrations of the C–H bond can lag behind other processes in the direction of bond cleavage and run ahead in the direction of bond formation. This imbalance is in the same direction as has been calculated for the addition of ammonia to formaldehyde.[54]

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Secondary α-Deuterium Isotope Effects for the Cleavage of Formaldehyde Hemiacetals through Concerted and Specific-Base-Catalyzed Pathways[1]

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Abstract: The observed secondary α-deuterium isotope effects for catalysis by acetate ion of the cleavage of formaldehyde hemiacetals increase from $k_{2H}/k_{2D} = 1.23$ to 1.28 to 1.34 with decreasing pK of the leaving alcohol in the series ethanol, chloroethanol, and trifluoroethanol. The pH-independent reaction shows a smaller isotope effect of 1.15–1.14 for the ethyl and chloroethyl hemiacetals. These reactions involve general-base catalysis of alcohol attack in the addition direction and the kinetically equivalent cleavage of the hemiacetal anion with general-acid catalysis by acetic acid or the proton in the cleavage direction. The results indicate that the amount of C–O cleavage in the transition state increases with decreasing pK of the alcohol and increasing pK of the acid catalyst, corresponding to a negative coefficient $p_{yy'} = \partial \rho_n / -\partial \mathrm{p}K_{lg} = \partial \beta_{lg} / -\partial \sigma$ and a positive coefficient $p_{xy} = \partial \rho_n / -\partial \mathrm{p}K_{HA} = \partial \alpha / \partial \sigma$. These results provide additional support for a concerted reaction mechanism with an important role of proton transfer in the transition state. Qualitative and semiquantitative characterizations of the transition state are presented in terms of reaction coordinate diagrams that are defined by the structure-reactivity parameters. The properties of the transition state suggest that the reaction is best regarded as an electrophilic displacement on the oxygen atom by the proton and by the carbonyl group in the cleavage and addition directions, respectively. The large secondary isotope effect of $k_{2H}/k_{2D} = 1.63$ for cleavage of the chloroethyl and trifluoroethyl hemiacetals catalyzed by hydroxide ion indicates a late transition state for alkoxide expulsion from the hemiacetal anion.

It has been shown that (kinetic) general-base catalysis of the reversible addition of water and alcohols to formaldehyde represents true general-base catalysis of the attack of ROH in the addition direction and the kinetically equivalent general-acid catalysis of the cleavage of the hydrate or hemiacetal anion in the reverse direction, according to the class n mechanism shown in eq 1.[2] This mechanism is a general one for catalysis of the reversible addition of water and alcohols at electrophilic carbon centers. Structure-reactivity correlations and the estimated

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