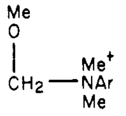
step of benzaldehyde semicarbazone formation follows ρ_n, not ρ, indicating that there is little or no electron donation by resonance or rehybridization in the transition state, although there is a large amount of resonance stabilization in the protonated imine product.[11] (3) An early transition state 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 $k_H/k_D = (1.07–1.08)/D$.[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]


$\mathrm{MeO{-}CH_2{-}N^{+}MeMeAr}$

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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 p*K* 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 p*K* of the alcohol and increasing p*K* of the acid catalyst, corresponding to a negative coefficient $p_{yy'} = \partial \rho_n / -\partial pK_{lg} = \partial \beta_{lg} / -\partial \sigma$ and a positive coefficient $p_{xy} = \partial \rho_n / -\partial pK_{HA} = \partial \alpha / \partial \sigma$. 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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[1] Supported by grants from the National Science Foundation (Grant PCM-7708369) and the National Institutes of Health (Grants GM20888 and GM20168). J.L.P. was a fellow of the American Cancer Society (No. PF-1465).

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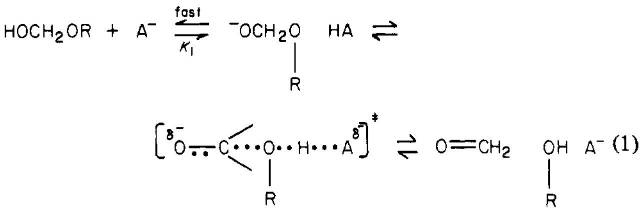

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lifetimes of intermediate species that would have to be formed in a stepwise reaction mechanism provide evidence that cleavage of the C–O bond and proton transfer to the leaving oxygen atom in the formaldehyde reactions are in some sense concerted.[2]

A concerted reaction mechanism could involve (1) primarily C–O bond cleavage with the proton in a single or rapidly equilibrating double well,[3] (2) primarily proton transfer,[4,5] or (3) both C–O cleavage and proton transfer that are somehow coupled in the transition state. Previously reported structure-reactivity correlations demonstrated changes in transition-state structure with varying leaving groups and catalysts that provide evidence for a coupling or interaction of the changes in bond length and support the fully concerted mechanism 3.[2] These interactions involve changes in the amount of proton transfer from the catalyzing acid and in the development of charge on the central oxygen atom of the leaving group with changing substituents at these positions. The most characteristic of these changes is an increase in the Brønsted α value with increasing pK of the central oxygen atom and a corresponding decrease in β_{lg} with increasing acidity of the catalyst.

We describe here the effects of changing structures of the leaving group and the acid catalyst on the amount of C–O bond cleavage in the transition state, as measured by secondary α-deuterium isotope effects. This provides a measure of the interaction of the central atom with one of the end atoms that is complementary to the previously reported[2] interaction of the central atom with the end atom of the acid catalyst at the other end of the transition state (**1**). It appeared possible that the very large changes in structure-reactivity parameters and bond length that have been observed at the latter end reflect some special property of the three-atom system including the proton, O···H···A, that gives rise to large changes in bond length with a relatively small perturbation of reactant structure. We were, therefore, curious whether similar changes occur at the C···O end of the system and whether such changes could provide further information about the structure of the transition state. The results provide additional support for the coupled mechanism 3, with an important component of proton transfer in the transition state. We also summarize briefly the characterization of transition states for this type of reaction through the use of reaction coordinate-energy contour diagrams to describe observed structure-reactivity interactions.[6]

Experimental Section

Materials. Stock solutions of formaldehyde and dideuterioformaldehyde were prepared by hydrolysis of 1 g of paraformaldehyde (Fisher) in 1 mL of water or 1 g of dideuterioparaformaldehyde (99.8%, ICN) in 1 mL of deuterium oxide, each containing 0.1 mmol of hydrochloric acid, for 3.5 h at 100 °C in a sealed ampule. The solution was treated with 1 g of Dowex 1 hydroxide to remove acid, diluted with water to 1 M, and used within 1 week after treatment with Dowex 1. The concentration of formaldehyde was determined by titration of the base liberated upon addition of sodium sulfite.[7] Semicarbazide hydrochloride and hydrazine monohydrochloride were recrystallized, 2,2,2-trifluoroethanol was distilled, and 2-chloroethanol was distilled at 10 mm.

Ethanol and trifluoroethanol hemiacetals were prepared by the addition of 5 μL of the appropriate formaldehyde stock solution to 1 mL of alcohol containing 4 μL of 1 M sodium hydroxide or 1.25 μL of 5 M imidazole–acetic acid (1:0.5) buffer.[2] Aliquots of these solutions were used between 3 and 24 h after preparation to initiate kinetic experiments. The chloroethanol hemiacetal was prepared similarly, but with 1.25 μL of 5 M imidazole–acetic acid (1:0.9) buffer, and was used between 3 and 8 h after preparation. Experiments with hemiacetals of methoxyethanol did not give satisfactory first-order kinetics and are not reported; methoxyethanol preparations were found by LC to contain an impurity that was not removed by five distillations.

Kinetics. Rate constants for buffer catalysis of hemiacetal cleavage were determined spectrophotometrically at 240 nm, 25 °C, ionic strength 1.0 M (KCl) by trapping free formaldehyde as the semicarbazone in the presence of 0.01 M semicarbazide.[2] Absorbance measurements (40–60 per run) were made at 0.2–2.0 min intervals by using a Zeiss PM6 spectrophotometer equipped with a digital printer. Pseudo-first-order rate constants were determined at 7–10 concentrations of potassium acetate buffer with alternating sets of 4 runs for the protium and deuterium compounds; the 14–20 runs for one determination of a secondary isotope effect were carried out in 1 day. Buffer ratios were chosen to give >88% general-base catalysis. Rate constants for catalysis by hydroxide ion of the cleavage of the chloroethyl hemiacetal were determined similarly at 230 nm by using hydrazine as a trapping reagent in four concentrations of 0.02–0.10 M potassium phosphate buffer or 0.01–0.08 M hydrazine buffer.

Pseudo-first-order rate constants and second-order rate constants for buffer catalysis were obtained by weighted least-squares analysis of plots of ln $(A_\infty - A_t)$ against time or k_{obsd} against buffer concentration, respectively, using eq 2–6,[8] in which $\bar{y}_i$ is the calculated value of y_i.

$$\text{slope} = [(\textstyle\sum w_i)(\sum w_i x_i y_i) - (\sum w_i x_i)(\sum w_i y_i)]/D \qquad (2)$$

$$\text{intercept} = [(\textstyle\sum w_i y_i)(\sum w_i x_i^2) - (\sum w_i x_i)(\sum w_i x_i y_i)]/D \qquad (3)$$

$$\sigma \text{ slope} = [(\textstyle\sum w_i)(\sum w_i(\bar{y}_i - y_i)^2)/D]^{1/2} \qquad (4)$$

$$\sigma \text{ intercept} = [(\textstyle\sum w_i x_i^2)(\sum w_i(\bar{y}_i - y_i)^2)/D]^{1/2} \qquad (5)$$

$$D = (\textstyle\sum w_i)(\sum w_i x_i^2) - (\sum w_i x_i)^2 \qquad (6)$$

Weighting factors, w_i, were obtained from standard deviations, σ_i, of the ith measurement according to $w_i = 1/\sigma_i^2$. Values of k_{obsd} (slope) and its standard deviation (σ slope) were calculated from eq 2 and 4 by assuming an error of 0.004A in the absorbance change, $\Delta A = A_\infty - A_t$, for determination of first-order rate constants; i.e., $\sigma_t = \ln\,[(\Delta A_t + 0.004)/\Delta A_t]$.[9] Values of A_∞ were calculated by computer to give the smallest deviation of the slope and were found to vary randomly from the measured end point by <0.003A. The experimental points fit the calculated slope within <0.005A and usually within <0.002A over >5 half-times, giving rate constants with 1–2.2% standard deviations. Plots of k_{obsd} against buffer concentration based on eq 2–6 typically showed 1–7% error (standard deviation/slope or intercept times 100%) for both slope and intercept. The values of w_i were obtained from the standard deviations of k_{obsd}. Secondary isotope effects were calculated from these slopes and intercepts according to eq 7,[10] in which A and B are the rate constants

$$\frac{A \pm a}{B \pm b} = \frac{A}{B}\left[1 + \sqrt{\left(\frac{a}{A}\right)^2 + \left(\frac{b}{B}\right)^2}\right] \qquad (7)$$

for cleavage of the protium and deuterium hemiacetals, respectively, and a and b are standard deviations. Weighted means, $\bar{x}$, and standard deviations, $\bar{\sigma}$, from several determinations were calculated from $\bar{x} = (\sum x_i w_i)/\sum w_i$ and $\bar{\sigma}^2 = \sum w_i(\bar{x} - x_i)^2/\sum w_i$.

Results

Typical determinations of pseudo-first-order rate constants and of second-order rate constants for catalysis of the cleavage of formaldehyde hemiacetals by acetate buffers are shown in Figures 1 and 2, respectively. Secondary α-deuterium isotope effects for the buffer-catalyzed and the buffer-independent reactions were obtained as described in the Experimental Section and are summarized in Table I. The rate constants for the protium compounds were found to agree closely with those reported previously.[2] The isotope effects for the buffer-independent "water" reaction of the

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(9) Although the choice of 0.004A as the estimated error in measuring ΔA is arbitrary, this introduces little error in the calculations. Substituting values of 0.006- or 0.002 A as the estimated error did not change the calculated slope or end point and changed the percent error of the slope (σ slope/slope × 100%) by <0.006%.

(10) Reference 8, p 140, as derived by Dr. Peter Heller.

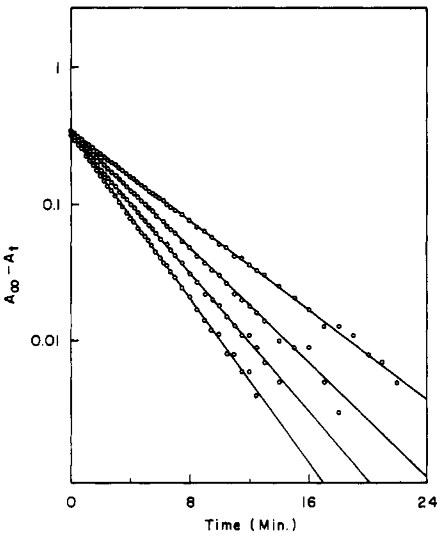

Figure 1. Computer-generated, weighted least-squares plot of the observed absorbance changes for the cleavage of trifluoroethyl formaldehyde hemiacetal catalyzed by acetate buffers, 0.05–0.35 M, in the presence of 0.01 M semicarbazide at ionic strength 1.0 M (KCl), 25 °C.

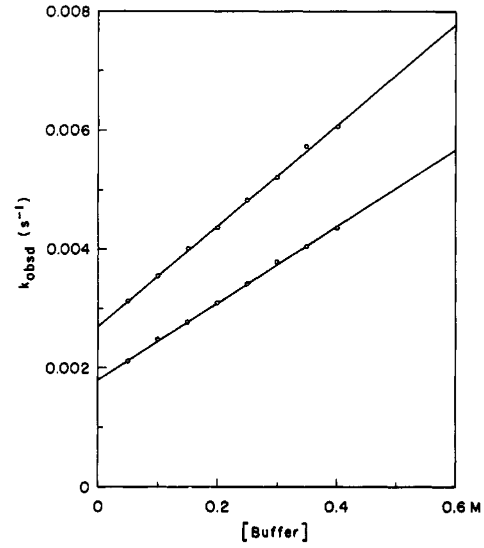

Figure 2. Typical weighted least-squares plots of the pseudo-first-order rate constants for cleavage of formaldehyde hemiacetals. The upper and lower lines are for the trifluoroethyl protium and deuterium formaldehyde hemiacetals, respectively, in acetate buffer, 30% anion, at ionic strength 1.0 M (KCl), 25 °C.

Table I. Secondary α-Deuterium Isotope Effects for Decomposition of Dideuterioformaldehyde Hemiacetals

% acetate anion	k_{HA}[a] (±)	k_{HOH}[b] (±)
	Ethanol Hemiacetal	
90	1.244 (0.080)	1.161 (0.056)
92.5	1.230 (0.060)	1.135 (0.053)
94	1.237 (0.099)	1.138 (0.066)
95	1.216 (0.061)	1.170 (0.048)
wtd av	1.229 (0.010)	1.153 (0.015)
	Chloroethanol Hemiacetal	
70	1.285 (0.125)	1.163 (0.105)
85	1.263 (0.108)	1.198 (0.095)
90	1.276 (0.063)	1.251 (0.073)
wtd av	1.275 (0.007)	1.142[c] (0.008[c])
	Trifluoroethanol Hemiacetal	
20	1.362 (0.062)	1.427 (0.035)
20	1.350 (0.120)	1.450 (0.092)
25	1.277 (0.077)	1.468 (0.059)
30	1.358 (0.169)	1.442 (0.093)
30	1.332 (0.061)	1.496 (0.045)
40	1.379 (0.162)	1.486 (0.082)
50	1.325 (0.184)	1.576 (0.063)
wtd av	1.336 (0.032)	1.619[d] (0.060[d])

[a] Isotope effect per two deuterons, $k(HOCH_2OR)/k(HOCD_2OR)$, for decomposition of formaldehyde hemiacetals catalyzed by acetate buffers at 25 °C, ionic strength 1.0 M (KCl). [b] Isotope effect per two deuterons on the buffer-independent reaction. [c] Extrapolated to 100% water-catalyzed reaction;[2,11] see text. [d] Extrapolated to 100% hydroxide-catalyzed reaction.[2,11]

Table II. Decomposition of Chloroethanol Hemiacetals Catalyzed by Hydroxide Ion[a]

catalyst	compd[b]	$10^3 k_{OH}$,[c] s^{-1} (±)	isotope effect
hydrazine[d]	H	9.332 (2.82×10^{-5})	
	D	5.736 (1.76×10^{-4})	1.627 ± 0.050
hydrazine[e]	H	8.079 (2.68×10^{-4})	
	D	4.817 (2.35×10^{-4})	1.677 ± 0.099
phosphate[f]	H	6.592 (2.15×10^{-4})	
	D	3.922 (1.90×10^{-4})	1.681 ± 0.098

[a] Reactions contained 0.01–0.10 M catalyst; ionic strength 1.0 M (KCl), 25 °C. [b] Abbreviations: H, formaldehyde chloroethanol hemiacetal; D, dideuterioformaldehyde chloroethanol hemiacetal. [c] Observed first-order rate constant of the buffer-independent reaction, which represents >90% hydroxide-ion catalysis at the pH values of the experiment.[2] [d] pH 7.21. [e] pH 7.15. [f] pH 6.94. The formaldehyde product was trapped with 0.01 M hydrazine.

Table III. Secondary α-Deuterium Isotope Effects for Decomposition of Formaldehyde and Dideuterioformaldehyde Hemiacetals[a]

	catalyst		hydroxide ion
leaving alcohol	acetate	water	
ethanol	1.23 ± 0.01	1.15 ± 0.02	
γ[b]	0.21	0.09	
2-chloroethanol	1.28 ± 0.01	1.14 ± 0.01	1.64 ± 0.02
γ	0.28	0.07	0.75
2,2,2-trifluoroethanol	1.34 ± 0.03		1.62 ± 0.06
γ	0.38		0.72

[a] Observed rate constant ratios, $k(HOCH_2OR)/k(HOCD_2OR)$, measured at 25 °C, ionic strength 1.0 M (KCl). The isotope effect with acetate catalysis represents kinetic general-base catalysis. The isotope effects are weighted averages of all experiments except for water-catalyzed chloroethyl hemiacetal and hydroxide ion catalyzed trifluoroethyl hemiacetal decomposition, which were determined by extrapolation as described in the text. [b] Fraction of C-O cleavage in the transition state, estimated from the isotope effects as described in the text.

chloroethyl hemiacetal and for catalysis by hydroxide ion of the cleavage of the trifluoroethyl hemiacetal were obtained from plots of the observed isotope effects against the fraction of the observed buffer-independent rate constants contributed by the water or hydroxide ion reaction. These plots are linear and the observed isotope effects represent >70% of the water and hydroxide ion reactions for the chloroethyl and trifluoroethyl hemiacetals, respectively, at the most unfavorable buffer ratios.[11] The rate constants and isotope effects for catalysis by hydroxide ion of the cleavage of the chloroethyl hemiacetal were determined in separate experiments and are given in Table II. The isotope effects are summarized in Table III.

Estimation of the Amount of Bond Cleavage. The amount of cleavage of the C–O bond in the transition state for hemiacetal cleavage was estimated from $k_H/k_D = E^\gamma$, in which E is the equilibrium secondary α-deuterium isotope effect for the reaction and γ is the fraction of reaction that has taken place in the transition state, as measured by the secondary isotope effect.[12]

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(11) Such plots of isotope effects, which are ratios of rate constants, are not exactly linear in principle, but are nearly linear for small extrapolations. Calculated curves showed an error from nonlinearity of ≤0.02 in the extrapolated isotope effect. The data were treated in this way because the isotope effect at each buffer ratio was determined in a series of paired experiments; plots of the individual rate constants for the protium and deuterium compounds from different experiments give a much larger error.

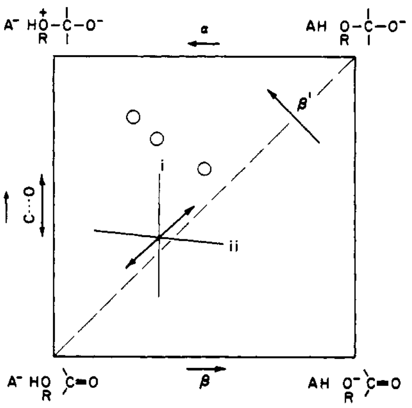

Figure 3. Reaction coordinate diagram for the cleavage of formaldehyde hemiacetals with proton transfer (α) along the x axis, C–O cleavage ($\gamma = 1 - \rho_n$) along the y axis and charge development on the leaving group (β_{lg}, β') along a diagonal axis.[2] The reaction coordinate is drawn to bisect two "level lines" of constant energy that pass through the saddle point. The circles describe the position of the transition states for reactions of the ethyl, 2-chloroethyl, and 2-trifluoroethyl hemiacetals (proceeding from left to right), based on the observed secondary isotope effects ($\rho_n = 1 - \gamma$) and Brønsted α values. The contour lines are omitted for clarity.

The value of E was taken as $1.31 = 1.37/1.05$, on the basis of the equilibrium isotope effects of 1.37 ± 0.02 for the cleavage of addition compounds of acetaldehyde, pentanal, and benzaldehydes with water or amines,[12-15] and a value of $K_H/K_D = 1.05$ (per deuterium) to correct for the isotope effect on the initial ionization of the hemiacetal to the hemiacetal anion (K_1, eq 1). This correction reflects the influence of the apparent electron-donating effect of deuterium compared with protium and is based on the dissociation constants of protonated amines.[16,17] The kinetic isotope effect per deuterium atom for cleavage of the hemiacetal anion was taken to be $k_H/k_D = R^{1/2}/1.05$, in which R is the observed ratio of the rate constants for $HOCH_2OR$ and $HOCD_2OR$ (Table III) and 1.05 is a correction for ionization of the hemiacetal to its anion, as described above. The values of γ are given in Table III. The values of ρ_n, a normalized measure of the amount of bond formation in the transition state for attack of the alcohol on formaldehyde, are equal to $1.0 - \gamma$.

Discussion

The increase in the observed secondary α-deuterium isotope effect from 1.23 to 1.34 as the leaving group is changed from ethanol to trifluoroethanol (Table III) indicates that there is an increase in the amount of C–O bond cleavage in the transition state for the breakdown of formaldehyde hemiacetals catalyzed by acetate buffers as the leaving group becomes more acidic. This change is described by a negative value of the coefficient[6] $p_{yy'}$ for this reaction according to eq 8, in which ρ_n is a measure of C–O

$$p_{yy'} = \frac{\partial \rho_n}{-\partial pK_{lg}} = \frac{\partial \beta_{lg}}{-\partial \sigma} \tag{8}$$

bond formation or cleavage and pK_{lg} is the pK of the leaving alcohol. It is convenient to describe this kind of reaction with a reaction coordinate-energy contour diagram (Figure 3) in which the coordinates are defined by structure-reactivity parameters such as α or β (for proton transfer, along the x axis), ρ_n (for C–O cleavage and formation, on the y axis) and β_{lg} or β_{nuc} (for substituents on the alcohol, on the diagonal axis, β' or y').[6,18] The reaction proceeds by breakdown of the hemiacetal anion (upper right corner) with proton donation to the leaving alcohol from the acid catalyst to give formaldehyde and the alcohol (lower left corner); in the reverse direction it involves general-base catalysis of alcohol addition (eq 1).[2]

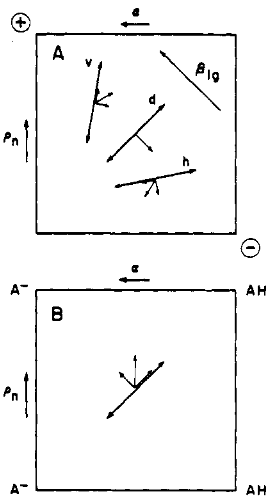

Figure 4. (A) Reaction coordinate-energy diagram to show the effect on the position of the transition state of an electron-withdrawing substituent on the leaving group that raises the energy of the upper left corner and lowers the energy of the lower right corner of the diagram, for different orientations of the reaction coordinate. (B) Diagram to show the effect on the position of the transition state of an increase in acid strength that raises the energy of the right side relative to the left side of the diagram.

These contour diagrams provide an empirical way to characterize transition states and reaction mechanisms in terms of structure-reactivity correlations, isotope effects, and other experimental parameters. To the extent that these parameters provide a measure of bond order or bond length the diagrams provide a description of the behavior of these quantities in different reactions.[6] It is important to emphasize that the relationships between these quantities are generally not linear and that deductions from these quantities do not provide a description of reaction trajectories or reaction coordinates on mass-weighted energy surfaces. Nevertheless, we suggest that the diagrams do provide a useful method to describe transition states and differences in the properties of transition states in different reactions. The effect of a polar substituent on a rate constant is a measure of the electrostatic interaction between the dipole of the substituent and the change in electron density that is "seen" by the substituent upon reaching the transition state. These changes result from changes in electron distribution accompanying the formation and cleavage of σ and π bonds. Interpretations of the physical properties of transition states from substituent effects and other experimental parameters rest on the assumption that changes in the parameters reflect these changes in electron distribution, bond order, and bond length. If this assumption is correct, the observation of a correlation or coupling of these changes means that there is a corresponding correlation or coupling of changes in bond order and length.

The amounts of bond cleavage in the transition state for the cleavage of formaldehyde hemiacetals, $\gamma = 1 - \rho_n$, were estimated from the observed secondary isotope effects as described in the Results section and Table III. This measure of bond cleavage may not have a linear relationship to estimates based on other parameters,[19] but we will define γ and ρ_n in terms of the secondary

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(17) DeFrees, D. J.; Bartmess, J. E.; Kim, J. K.; McIver, R. T., Jr.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6451–6452. DeFrees, D. J.; Hassner, D. Z.; Hehre, W. J.; Peter, E. A.; Wolfsberg, M. *Ibid.* **1978**, *100*, 641–643.

(18) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274–277.

(19) Palmer, J.; Jencks, W. P., preceding article in this journal.

isotope effect criterion for the purposes of this discussion. The changes in the position of the transition state with changing pK of the leaving group are shown as the open circles in Figure 3, on the basis of the observed values of ρ_n and α.[2] These and other changes in the position of the transition state on this diagram with changing substituents on the reactants are consistent with the diagonal reaction coordinate of a concerted reaction mechanism that has been proposed previously for this reaction.[2]

The results may be accounted for qualitatively as shown in Figure 4A. Consider the reaction coordinates v, d, and h that pass in predominantly vertical, diagonal, and horizontal directions through saddle points that have similar curvatures perpendicular and parallel to the reaction coordinate (the contour lines have been omitted from this diagram for clarity). A substituent that increases the energy of a reactant will cause a transition state to slide downhill, away from the increase in energy, in the direction perpendicular to the reaction coordinate and to climb uphill, toward the increase in energy, in the direction parallel to the reaction coordinate (a "Hammond effect").[20] An electron-withdrawing substituent on the leaving alcohol raises the energy of the protonated alcohol in the upper left corner and lowers the energy of the alcoholate anion in the lower right corner of the diagram. This tilts the surface so that the saddle point and transition state of the diagonal reaction coordinate, d, slide downhill toward the lower right corner, perpendicular to the reaction coordinate. The downward component of this movement corresponds to an increase in C–O cleavage on the ρ_n scale of the y axis, consistent with the observed increase in secondary isotope effect. A predominantly vertical reaction coordinate (v) will give a smaller perpendicular shift and a shift, parallel to the reaction coordinate, toward the increased energy of the upper left corner (a "Hammond" shift). The resultant of these shifts will move the transition state toward the top of the diagram in the direction of less C–O cleavage, in the opposite direction from the observed change in secondary isotope effect. A predominantly horizontal reaction coordinate (h) will give a downward movement and a shift to the left, away from the decreased energy of the lower right corner.

The same shifts show the effects of an electron-withdrawing substituent in the alcohol on the amount of proton transfer and on the charge development of the leaving alcohol, as described by the changes in the Brønsted α coefficient (eq 9) and β_{lg} (eq 10).[2] The observed decrease in α with electron-withdrawing

$$p_{xy'} = \partial \alpha / \partial \mathrm{p}K_{lg} = \partial \beta_{lg} / -\partial \mathrm{p}K_{HA} \tag{9}$$

$$p_{y'} = \partial \beta_{lg} / -\partial \mathrm{p}K_{lg} \tag{10}$$

substituents on the leaving group (positive $p_{xy'}$) corresponds to movement of the transition state toward the right and is consistent with the diagonal and predominantly vertical reaction coordinates, d and v, but not the predominantly horizontal reaction coordinate, h. The decrease in β_{lg} with electron-withdrawing substituents (negative $p_{yy'}$ or "anti-Hammond" effect) corresponds to movement of the transition state toward the lower right corner and is consistent with the diagonal reaction coordinate. The movements with predominantly vertical or horizontal reaction coordinates, v or h, are smaller but are not necessarily inconsistent with this result.

The pH-independent "water" reaction proceeds by the same mechanism as the other general-base-catalyzed reactions (eq 1) and involves cleavage of the hemiacetal anion with general-acid catalysis by the proton in the breakdown direction.[2] The secondary isotope effect decreases from 1.23 to 1.28 for catalysis by acetic acid to 1.14–1.15 for catalysis by the proton in the "water" reaction (Table III). This indicates that the amount of C–O bond cleavage in the transition state decreases with increasing strength of the catalyzing acid, as described by a positive p_{xy} coefficient (eq 11).

$$p_{xy} = \partial \rho_n / -\partial \mathrm{p}K_{HA} = \partial \alpha / \partial \sigma \tag{11}$$

This result is also consistent with a diagonal reaction coordinate but is not expected for completely vertical or horizontal reaction coordinates.[6] An increase in acid strength raises the energy of the right side relative to the left side of the diagram, which causes the transition state of a diagonal reaction coordinate to slide downhill toward the upper left corner, perpendicular to the reaction coordinate, and to move uphill toward the upper right corner, parallel to the reaction coordinate (Figure 4B). The resultant of these shifts will be a net upward movement, corresponding to the observed decrease in C–O bond cleavage, and a cancellation of the movements to the right and left, so that there will be only a small or no change in the amount of proton transfer, as measured by α. The latter result is also consistent with the data.[2]

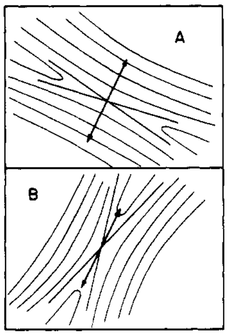

Figure 5. Reaction coordinates and level lines of constant energy passing through saddle points on a narrow ridge (A) and in a narrow pass (B). The angles of the level lines determine the orientation of the reaction coordinate and the ratio of the curvatures parallel and perpendicular to the reaction coordinates.

Thus, the changes in secondary isotope effects provide additional support for a concerted reaction mechanism with a predominantly diagonal reaction coordinate. They are difficult or impossible to reconcile with a vertical reaction coordinate that represents only C–O cleavage in the transition state, with the catalyst providing stabilization by hydrogen bonding. In particular, they show that the large shifts in β_{lg} with changing acid strength and in α with changing pK of the leaving group that are described by the $p_{xy'}$ coefficient do not represent a special effect that is made possible by facile movement of the proton relative to A^- and the central atom in a loose transition state. The negative $p_{yy'}$ coefficient shows that analogous (although smaller) changes take place in the relationship between the central oxygen atom and the formaldehyde carbon atom.

Semiquantitative Treatment. A more rigorous characterization of the transition state in terms of structure-reactivity parameters can be made assuming parabolic curvatures of the surface around the saddle point and a linear relationship between small perturbations of the energy at the edges and corners of the diagram and at the saddle-point region.[6] This approach does not require a knowledge of the complete energy surface. The properties of the saddle point and transition state are determined in large part simply by the signs of the structure-reactivity interaction coefficients; they can be described quantitatively if several of these coefficients are known.

A saddle point has two lines of constant energy that proceed out from the center with neither upward nor downward curvature ("level lines"), and the reaction coordinate is usually assumed to bisect these lines (Figure 5). The positions of these lines provide the simplest means of characterizing the transition state and its structure-reactivity behavior. The movement of a transition state at a saddle point with changing structure of the reactants depends on the orientation of the reaction coordinate and saddle point (Figure 4A) and on the curvatures of the surface parallel and perpendicular to the reaction coordinate. For a given direction of the reaction coordinate, tilting the surface will cause the transition state to move a large distance when the curvature is small (perpendicular to the reaction coordinate in Figure 5A and parallel to the reaction coordinate in B) and to change very little when the curvature is steep (parallel and perpendicular to the reaction coordinates in parts A and B, respectively).[6,20] The position of the level lines defines the orientation of the saddle point

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

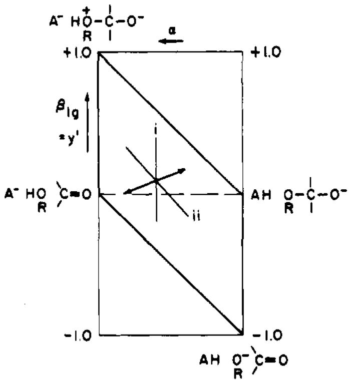

Figure 6. Transformed diagram with perpendicular axes for proton transfer and β_{1g}. The reactants and products are connected by the dashed line.

and the *ratio* of these two curvatures. When the two curvatures are quite different, as in Figure 5A,B, shifts in the position of the transition state cannot be predicted simply from the direction of the reaction coordinate, because the amounts of the shifts parallel and perpendicular to the reaction coordinate will be different from those observed when the two curvatures are equal (Figure 4).

Changes in the directions of the level lines reflect changes in the amount and the sign of the curvatures parallel to the x and y axes (Figure 5). These changes give rise to changes in the amount and the direction of movement of the transition state with changing structure of the reactants, i.e., to changes in the magnitude and the sign of the structure-reactivity interaction coefficients, such as $p_{yy'}$. Conversely, the structure-reactivity and interaction coefficients define the position, orientation, and curvatures of the saddle point, so that the transition state can be characterized in terms of this energy diagram by experimental determination of these coefficients.[6]

We will describe the properties of the transition state for the cleavage of formaldehyde hemiacetals according to eq 1 on the basis of these interaction coefficients. The earlier experimental data and the relationship of these coefficients to the geometry of the energy diagram in the following are described in ref 2 and 6, respectively. The calculated level lines and direction of the reaction coordinate from the previous work are shown in the square diagram of Figure 3.

The negative sign of $p_{y'} = \partial\beta_{1g}/-\partial pK_{1g} = -0.20$ corresponds to an "anti-Hammond" effect for the leaving group, as described above (Figure 4A.*d*). The saddle point is characterized by the curvatures a and b, parallel to the x and y axes, respectively, and the diagonal curvature c on the energy surface of the diagram of Figure 3. It is convenient to describe effects involving the leaving group (the central atom in this reaction) by a transformed diagram in which the charge on the leaving group, as measured by β_{1g}, is on the vertical axis, y', and proton transfer is on the horizontal axis (Figure 6); the curvatures in this diagram are a', b', and c'.

The negative sign of $p_{y'}$ means that the horizontal curvature a' is negative in the transformed diagram of Figure 6 so that the level line *ii*, which has zero curvature, must be rotated clockwise from the horizontal (Figure 6). The negative horizontal curvature a' is required by the relationship between the structure-reactivity coefficient and the geometry of the energy surface, which is described by $p_{y'} = -2a'/(4a'b' - c'^2)$, and by the negative sign of $4a'b' - c'^2$ (the term $4a'b' - c'^2$ must be negative for surfaces that describe a saddle point). Level line *ii* must be rotated clockwise from the horizontal because the curvature is downward (negative) along the reaction coordinate and in the horizontal direction; it remains downward until the level line of zero curvature is reached. If the other level line is close to vertical (see below), this means that the reaction coordinate must have a large horizontal component, corresponding to proton transfer. This result *is inconsistent with a vertical reaction coordinate, in which the* proton is in a well and there is only C–O cleavage in the transition state. A level line that is rotated clockwise from the horizontal on the transformed diagram (Figure 6) corresponds to a line that is rotated clockwise from the diagonal (the dashed line) on the square diagram, so that this is consistent with Figure 3.

General-acid catalysis of C–N cleavage in carbamate breakdown does appear to proceed through a near vertical reaction coordinate with hydrogen bonding to the leaving group, and this reaction has a positive $p_{y'}$ coefficient ("Hammond" behavior).[21] A positive $p_{y'}$ coefficient corresponds to a positive horizontal curvature, a', and to a level line *ii* that is rotated counterclockwise from the horizontal on the transformed diagram and counterclockwise from the diagonal on the square diagram.

The positive sign of $p_{xy'} = \partial\alpha/\partial pK_{1g} = \partial\beta_{1g}/-\partial pK_{HA} = 0.09$ means that the curvature c' is negative, from the relationship $p_{xy'} = c'/(4a'b' - c'^2)$. This corresponds to a reaction coordinate that proceeds from the lower left to the upper right quadrant in Figure 6. It ordinarily means that there is an important vertical component to the reaction coordinate in both the transformed and the square diagrams.

When $p_{xy'}$ is positive the reaction coordinate can approach a horizontal direction only if there is a strongly negative curvature a' and coefficient $p_{y'}$. These characteristics correspond to a saddle point on a narrow, vertical ridge in the diagram and to a transition state that involves mainly proton transfer.

A negative $p_{xy'}$ coefficient is possible when (and only when) the coefficient $b = b'$ is positive, i.e., when there is upward curvature in the vertical cross-section through the saddle point. If this requirement is not met, the reaction coordinate does not proceed in the direction from reactants to products in Figure 3.

The level lines and curvatures are more fundamental properties of these surfaces than a reaction coordinate that bisects the level lines. Comparison of Figures 6 and 3 shows that the reaction coordinate that bisects the level lines is rotated counterclockwise from the (dashed) horizontal line that directly connects the reactants and products in the transformed diagram but slightly clockwise from the corresponding dashed diagonal line in the square diagram. This is a consequence of the nonlinear change in angles between the two diagrams.[6,22] The level lines, the movements of the transition state with changing structure of the reactants that are determined unambiguously by the geometry of the surface, and the corresponding structure-reactivity parameters are all invarient upon transformation of the diagram.

The Brønsted plots for hemiacetal cleavage and related reactions are generally linear so that the coefficient $p_x = \partial\alpha/\partial pK_{HA}$ is indistinguishable from zero. There is sometimes a negative deviation for catalysis by the proton that could reflect a positive p_x coefficient and a "Hammond effect" for proton transfer; negative p_x coefficients are rare if they occur at all in this type of reaction. A coefficient of $p_x = 0$ corresponds to a vertical level line *i* (Figures 3 and 6), from the relationship $p_x = -2b/(4ab - c^2)$. When $p_x = b = 0$, there is zero curvature in the vertical direction, parallel to the y axis, so that the level line of zero curvature is vertical. A positive p_x coefficient corresponds to positive curvature in the vertical direction and rotation of level line *i* clockwise from the vertical.

This is an important result, because it requires a significant diagonal component to the reaction coordinate and a significant component of proton transfer in the transition state. This diagonal character gives rise to partial or complete cancellation of the vectors for movement of the transition state parallel and perpendicular to the reaction coordinate along the x axis for proton transfer, as described above for the p_{xy} coefficient (Figure 4B), so that there is little or no change in α as the pK of the acid is changed. If the reaction coordinate were vertical, the large changes in the position of the proton with changing pK of the leaving group (large $\partial\alpha/\partial pK_{1g} = p_{xy'}$) should be accompanied by comparable changes with changing pK of the acid (large negative $\partial\alpha/\partial pK_{HA} = p_x$). This situation would correspond to a broad potential well

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(21) Ewing, S.; Lockshon, D.; Jencks, W. P. *J. Am. Chem. Soc.*, **1980**, *102*, 3072–3084.

(22) See also: Maggiora, G. M.; Christoffersen, R. E. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 119–163.

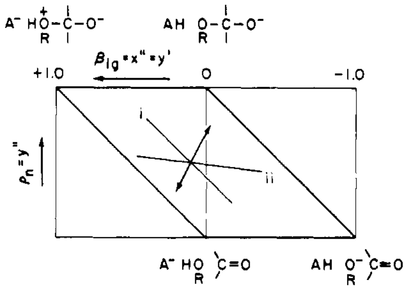

Figure 7. Transformed diagram with perpendicular axes for C–O formation and cleavage ($\rho_n = 1 - \gamma$) and for β_{lg}. The reactants and products are connected by the dashed line.

Table IV. Relationships of the Parameters of the Diagrams of Figures 3 and 7[a]

$x = y'' - x''$
$y = y''$

$a'' = a$
$b'' = a + b + c$
$c'' = -2a - c$
$d'' = -d$
$e'' = d + e$
$f'' = f$
$4a''b'' - c''^2 = 4ab - c^2$

[a] The double-primed symbols refer to the transformed diagrams of Figure 7. Note that d'' refers to the energy of the *left* edge of Figure 7. The parameters were calculated as described in Table II of ref 6. The coefficients for this transformation, with $x = ix'' + jy''$ and $y = mx'' + ny''$, are $i = -1, j = 1, m = 0$ and $n = 1$.

for the proton on a horizontal ridge across the diagram.

It is an interesting and surprising consequence of the geometry of the energy surface that whether Hammond or anti-Hammond behavior is observed for proton transfer is determined by whether there is a well or a maximum in the *vertical* cross section through the saddle point; i.e., by whether the vertical curvature b is positive or negative (this corresponds to rotation of the level line i of Figure 6 clockwise or counterclockwise from the vertical, respectively). It is not determined by whether there is a well or a maximum in the horizontal cross section through the saddle point that describes motion of the proton.

The $p_{yy'}$ coefficient is most easily described with a transformed diagram in which C–O cleavage is measured on the vertical axis ($\rho_n = 1 - \gamma$) and the effective charge on the leaving group (β_{lg}) is measured on the horizontal axis (Figure 7). The relationships of the coordinates and coefficients of this diagram to those of a square diagram are summarized in Table IV and eq 12–14. The

$$p_{y'} = p_{x''} = \frac{\partial x''}{\partial d''} = \frac{-2b''}{4a''b'' - c''^2} = \frac{-2(a + b + c)}{4ab - c^2} \quad (12)$$

$$p_y = p_{y'} = \frac{\partial y''}{\partial e''} = \frac{-2a''}{4a''b'' - c''^2} = \frac{-2a}{4ab - c^2} \quad (13)$$

$$p_{yy'} = p_{x''y''} = \frac{\partial x''}{\partial e''} = \frac{\partial y''}{\partial d''} = \frac{c''}{4a''b'' - c''^2} = \frac{-(2a + c)}{4ab - c^2} \quad (14)$$

curvatures and coefficients of this diagram are indicated by double primes. The transformations of these diagrams may be regarded as a downward movement of the right side of the square diagram for Figure 6 and a movement to the left of the top edge of the square diagram for Figure 7. *Note that the horizontal axis in Figure 7 ($x'' = y' = \beta_{lg}$) increases from right to left, in order to be consistent with the other diagrams. Consequently, the sign of the $p_{yy'}$ coefficient as originally defined[6] has been reversed, to maintain consistency among the three diagrams.*

A negative $p_{yy'}$ coefficient corresponds to a positive diagonal curvature c'' and to a reaction coordinate that proceeds from the lower left to the upper right quadrant of this diagram; a positive $p_{yy'}$ coefficient gives a negative c'' and a reaction coordinate that proceeds from the lower right to the upper left quadrant.

The secondary isotope effects and γ values in Table III give a value of $p_{yy'} = \partial\rho_n/-\partial pK_{lg} = -0.047$. The negative sign of this coefficient means that the diagonal curvature c'' for this diagram is positive, from the relationship $p_{yy'} = c''/(4a''b'' - c''^2)$. This corresponds to a diagonal reaction coordinate that proceeds from the lower left to the upper right quadrant in Figure 7. The value of $b = 0$ corresponds to a diagonal level line i on this diagram. These results require an important component of proton transfer and a significant horizontal component to the reaction coordinate. Level line ii must be rotated >45° clockwise from the vertical in Figure 7 and a corresponding amount clockwise from the diagonal in the square diagram of Figure 3. This is inconsistent with a hydrogen-bonding mechanism with the proton in a potential well.

A negative $p_{yy'}$ coefficient always requires an important horizontal component to the reaction coordinate when the vertical curvature b is 0 or positive. The reaction coordinate can approach vertical only when both level lines are close to horizontal and the saddle point is in the broad well of a narrow ridge across the diagram. This corresponds to the broad potential well of a hydrogen-bonding mechanism and should give a large, easily measurable negative p_x coefficient. A positive $p_{yy'}$ coefficient is possible when (and only when) the coefficient $a = a''$ is positive, i.e., when there is upward curvature in the horizontal cross section through the saddle point.

The proton-catalyzed hydrolysis of 2-(para-substituted phenoxy)tetrahydrofurans exhibits a *decrease* in secondary isotope effect from $k_H/k_D = 1.1$ for p-MeOPhO– to $k_H/k_D = 1.06$ for p-NO$_2$PhO– as the leaving group.[23] This indicates decreased bond cleavage with electron-withdrawing substituents on the leaving alcohol, which is the opposite behavior from that for formaldehyde hemiacetals and corresponds to a positive $p_{yy'}$ coefficient. A positive $p_{yy'}$ coefficient means that the reaction coordinate is rotated counterclockwise from the vertical in the transformed diagram of Figure 7 and is near vertical in the square diagram of Figure 3. Such a reaction coordinate represents primarily C–O bond cleavage in the transition state and, in the limit, corresponds to specific-acid catalysis with complete protonation prior to C–O bond cleavage. The change in transition-state structure is then a simple Hammond effect.[23] In fact, there is a progressive increase in the inverse solvent deuterium isotope effect with increasing pK of the leaving group, from $k_D/k_H = 1.33$, 2.48, and 2.82 in the series p-nitrophenol, p-methoxyphenol, ethanol, and a disappearance of detectable general-acid catalysis with the more basic leaving groups that reflects an increase in the Brønsted α coefficient.[4,24] These changes suggest that there is a progressive shift toward a transition state with more proton transfer and A-1 character and that with the most basic leaving groups the reaction proceeds by specific-acid catalysis. An increase in α is expected with increasing pK of the leaving group as a consequence of the positive p_{xy} coefficient that is characteristic of this class of reaction; it is also expected for a reaction that gives an unstable oxocarbonium ion rather than formaldehyde as the immediate product as a consequence of a positive p_{xy} coefficient (see below). Thus, it appears that when the reaction coordinate is forced over to the left-hand edge of the diagram, it is forced to become vertical and the reaction mechanism undergoes a transition to specific-acid catalysis.

The same conclusion is suggested by the change in the amount of C–O bond cleavage with changing substituents on the aldehydic carbon atom in acetal cleavage that is described by the p_y coefficient (eq 15). The proton-catalyzed cleavage of substituted

$$p_y = \partial\rho/-\partial\sigma \quad (15)$$

benzaldehyde diethyl acetals shows an increased secondary α-deuterium isotope effect with electron-withdrawing substituents, of $k_H/k_D = 1.04$, 1.09, and 1.15 for p-methoxy-, unsubstituted, and p-nitrobenzaldehyde acetals, respectively.[23] This corresponds

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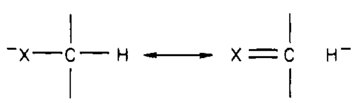
(23) Bull, H. G.; Koehler, K.; Pletcher, T. C.; Ortiz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1971**, *93*, 3002–3011.

(24) Fife, T. H.; Brod, L. H. *J. Am. Chem. Soc.* **1970**, *92*, 1681–1684.

to an increase in C–O bond cleavage, a positive p_y coefficient, and a predominantly vertical reaction coordinate if it does not represent a partial change in rate-limiting step.[25,26] A positive p_y coefficient corresponds to a positive horizontal curvature a on the square diagram of Figure 3, from the relationship $p_y = -2a/(4ab - c^2)$, to a level line *ii* that is rotated counterclockwise from the horizontal, and to a predominantly vertical reaction coordinate. A near-vertical reaction coordinate is consistent with specific-acid catalysis or general-acid catalysis with a large Brønsted α coefficient.[23,26] There is a similar increase in the secondary isotope effect for the dehydration step of semicarbazone formation from substituted benzaldehydes in the series unsubstituted, 3-bromo-, and 4-nitrobenzaldehyde[14,15] that suggests a positive p_y coefficient and a more vertical reaction coordinate than in the case of hemiacetal cleavage. However, this conclusion is uncertain in view of a decrease in the isotope effect for *p*-methoxybenzaldehyde semicarbazone formation and for phenylhydrazone formation compared with semicarbazone formation,[14,15] which would be expected to give a larger isotope effect if the p_y coefficient were positive.

The p coefficients are second derivatives of log k with respect to structural parameters and a change in the p coefficient, which corresponds to a change in the direction of the reaction coordinate, therefore represents a third derivative of log k. Such changes should—indeed must—occur but have not yet been treated quantitatively. The p coefficients are expected to be constant only so long as the orientation and curvature of the surface around the transition state are constant. This is unlikely to be the case for large changes in the position of the transition state so that these parameters will change with large perturbations of the surface, especially when the edge of the diagram is approached.

Deuterium substitution on an atom adjacent to an atom carrying a negative charge or lone-pair electrons gives an apparent electron-donating effect that has been attributed to relatively unfavorable negative hyperconjugation (**2**).[16,17] Although this effect may decrease the absolute magnitude of the observed α-deuterium isotope effect, by destabilizing the deuterium-substituted hemiacetal anion more than the transition state for its cleavage, it is unlikely that it has a large effect on the *change* in isotope effect that is taken as evidence for an increase in C–O bond cleavage with electron-withdrawing substituents on the leaving group. There is a decrease in β_{lg} with more acidic leaving groups, but this presumably involves withdrawal of electron density from the leaving oxygen atom that stabilizes the transition state and is not likely to increase the amount of negative hyperconjugation at the site of deuterium substitution. The value of $\beta_{\mathrm{lg}} = -0.58$ for trifluoroethanol would be even more negative if there were not some proton transfer to the leaving oxygen atom, so that there is a large amount of C–O bond cleavage and withdrawal of electron density from the carbon atom in the transition state. The total charge in the transition state remains constant with different leaving groups and the large decrease in β_{lg}, from +0.20 to –0.58, is itself difficult to explain unless there is increased C–O cleavage as well as decreased proton transfer in the transition state for expulsion of acidic alcohols.



$$^{-}X{-}C{-}H \longleftrightarrow X{=}C \quad H^{-}$$

2

The positive coefficient $p_{xy} = \partial\rho_{\mathrm{n}}/-\partial \mathrm{p}K_{\mathrm{HA}} = 0.027$ corresponds to a significant diagonal character to the reaction coordinate (Figures 3 and 4B), as expected for a concerted reaction mechanism. The positive p_{xy} coefficient means that the diagonal curvature c is negative, from the relationship $p_{xy} = c/(4ab - c^2)$, so that the reaction coordinate proceeds from the lower left to the upper right corner of the diagram. Zero diagonal curvature corresponds to a vertical or horizontal reaction coordinate, and a positive curvature corresponds to a reaction coordinate that leads from the upper left to the lower right quadrant of the diagram.

The quantitative significance of the positive p_{xy} coefficient is uncertain, because it is based on only two catalysts of different charge type. We believe that the p_{xy} coefficient is probably real and has a positive sign, but the possibility has not been rigorously excluded that the small secondary isotope effects for the proton-catalyzed reactions reflect a partially diffusion-controlled rate-determining step.[27] It should be noted that p_{xy} coefficients are generally small and difficult to measure, so that failure to detect a positive p_{xy} coefficient does not exclude a diagonal reaction coordinate.

Relationships between Different Structure-Reactivity Coefficients. Structure-reactivity coefficients that describe the effects of substituents in any *two* positions of the reactants can be described in a straightforward way with the appropriate reaction coordinate diagram. For example, the effects of substituents on the acid and on the aldehyde in hemiacetal cleavage (i.e., on the end atoms of this system) can be described by a diagram with α and ρ_{n} as the x and y coordinates and by the corresponding interaction coefficients p_x, p_y, and p_{xy}. Similarly, the effects of substituents on the acid and on the leaving group (the central atom in this system) can be described by a square or a transformed diagram with α and β_{lg} as coordinates and by the interaction coefficients p_x, $p_{y'}$, and $p_{xy'}$. However, it may or may not be possible to describe the effects of substituents in *three* different positions such as the acid, the aldehyde, and the leaving group with a single diagram. If it is possible, we can say that the different structural changes in the transition state are *balanced*; if it is not possible, these changes are *imbalanced* and it is necessary to describe the different changes on separate diagrams or with an additional dimension in a single diagram. Imbalance occurs when the changes in structure-reactivity parameters, and presumably bond orders, are not additive. It is of interest because it provides additional information about the nature of the transition state.

The interaction coefficients for the parameters described by the diagrams of Figures 3, 6, and 7 are related by eq 16–19, which

$$p_{y'} = p_x + p_y - 2p_{xy} \tag{16}$$

$$p_{yy'} = p_y - p_{xy} \tag{17}$$

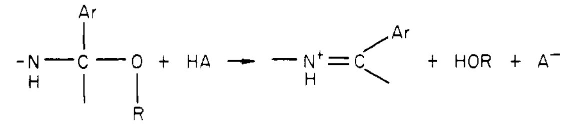
$$p_y = p_x + p_{y'} + 2p_{xy'} \tag{18}$$

$$p_{yy'} = p_{y'} + p_{xy'} \tag{19}$$

are obtained from eq 12–14, and the corresponding equations for p_x, p_y, $p_{y'}$, p_{xy}, and $p_{xy'}$.[6] An imbalance between the effects of substituents in the aldehyde, the leaving group, and the acid has been described previously for benzaldehyde semicarbazone and tosylhydrazone formation according to eq 20 (which is obtained

$$p_{xy'} = p_{xy} - p_x \tag{20}$$

from eq 16, 17, and 19).[28] The values of $p_{xy'} = 0.07$, $p_{xy} \leq 0.02$, and $p_x = 0$ for this reaction (eq 21) show that the effects of



$$-\underset{H}{N}-\overset{Ar}{C}-\underset{R}{O} + HA \longrightarrow -\underset{H}{N^{+}}{=}C\langle^{Ar} + HOR + A^{-} \tag{21}$$

increasing acid strength on the central atom (β_{lg}) are much larger than on the imine (ρ_{n}), so that all of these effects cannot be described by a single diagram. Part of the discrepancy represents an electrostatic effect, but most of it can be reasonably accounted for by an overall tightening or contraction of the transition state

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[25] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8248.

[26] Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672–4677.

[27] The rate constants for the "water" reactions fall close to the Brønsted lines for other general-base catalysts. In the cleavage direction this reaction represents cleavage of the hemiacetal anion catalyzed by the proton. The calculated rate constants for the individual proton-transfer steps of the reaction are close to the diffusion-controlled limit. The most likely explanation of these facts is that the proton transfers proceed by a "one-encounter" process, with rate-limiting general-acid catalysis of C–O cleavage by the proton according to the same mechanism as other catalysts.[2]

[28] Funderburk, L. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 6708–6714.

as the acid and the leaving oxygen atom come closer together when the acid becomes stronger or the leaving group becomes more basic ($p_{xy'} = \partial\beta_{lg}/-\partial pK_{HA} = \partial\alpha/\partial pK_{lg}$).[28]

A similar imbalance exists in the acid-catalyzed cleavage of benzaldehyde methyl phenyl acetals,[6,29] Meisenheimer complexes,[30] and formaldehyde hemiacetals. The values of $p_{xy'} = 0.09$, $p_{xy} = 0.027$, and $p_x = 0$ for hemiacetal cleavage give a nonadditivity of 0.063 unit. The probable errors in these parameters are not in the direction that would reduce this difference significantly. The p_y coefficient has been estimated previously to be −0.02, on the basis of eq 18 and $p_{y'} = -0.20$. There is then a large imbalance of −0.126 unit between the measured $p_{y'}$ value and the value of $p_{y'} = -0.074$ calculated from eq 16. These two imbalances are complementary and describe much larger changes in the bonding of the leaving group (the central atom) with the acid than with the aldehyde in the transition state. This is manifested directly in the larger absolute magnitude of $p_{xy'} = \partial\alpha/\partial pK_{lg} = 0.09$ compared with $p_{yy'} = \partial\rho_n/-\partial pK_{lg} = -0.047$. The imbalances and the large $p_{y'}$ and $p_{xy'}$ coefficients correspond to a net tightening of the transition state when the leaving alcohol becomes more basic and the acid moves closer to it, as described above for semicarbazone and tosylhydrazone formation.

The interaction of the aldehyde with the leaving group and with the acid, on the other hand, shows no detectable imbalance. The values of $p_{yy'} = -0.047$, $p_y = -0.02$, and $p_{xy} = 0.027$ agree with eq 17. This means that the increase in C–O cleavage with decreasing pK of the leaving group and with decreasing strength of the acid are consistent with each other. The shifts in the position of the transition state corresponding to these coefficients can be described either by the diagrams of Figures 3 and 7 or by a single diagram with three coordinates.

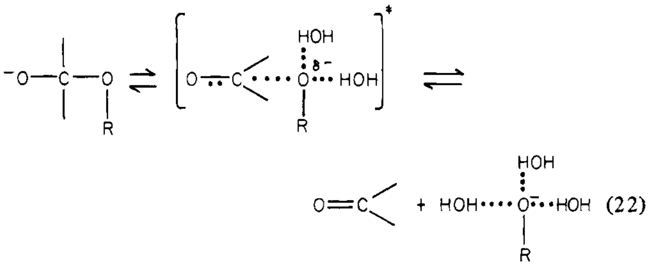
The reason for the simpler behavior of the aldehyde than of the acid is not known but might be a consequence of the additional bond that is cleaved when the acid donates a proton to the leaving alcohol. The carbonyl oxygen atom, which serves as a source or sink for electrons on one side of the reaction, always remains bonded to the carbon atom whereas A^-, which serves as a source or sink for electrons on the other side of the reaction, separates completely from the proton so that this side of the transition state may be more flexible.

Too much quantitative significance should not be attached to these comparisons because of the many uncertainties in the quantitative evaluation of the interaction coefficients, including experimental error, electrostatic interactions, solvation effects, and differing relationships of different experimental parameters to changes in bond order. However, we believe that the imbalances (and balances) described here are real and provide meaningful information about the properties of the transition state. The changes in β_{lg} and α that are described by the $p_{y'}$ and $p_{xy'}$ coefficients are large and changes in other parameters that would be required to fit eq 16 and 20 would be easily detectable. The agreement of the $p_{yy'}$, p_y, and p_{xy} parameters according to eq 17 is surprisingly good and provides some reassurance that these relationships hold in favorable cases.

The properties of the saddle point can be calculated from the observed structure-reactivity coefficients.[2,6] The observed values of $p_{yy'}$, p_x, and p_{xy} give a diagram with curvatures $a = -13.7$, $b = 0$, and $c = -37$, coordinate ratios of $g_1/g_2 = 0$ and −2.7 for the level lines, and a reaction coordinate that bisects these level lines and is rotated 55° clockwise from the vertical. The calculated value of $p_y = -0.02$ is also consistent with this diagram. These curvatures are larger than those that were calculated earlier from the $p_{xy'}$, $p_{y'}$, and p_x coefficients[2] because of the imbalance between the different coefficients. The relatively small $p_{yy'}$ and p_{xy} coefficients correspond to smaller movements of the transition state and, therefore, to larger curvatures of the surface. The larger curvatures correspond to values of $p_{xy'} = 0.027$ and $p_{y'} = -0.074$, approximately one-third of the observed values. The direction of the reaction coordinate, however, is very similar to the previously reported rotation of 48° clockwise from the vertical, which is based on the $p_{xy'}$, $p_{y'}$, and p_x coefficients.[2] Thus, Figure 3 gives a surprisingly close fit to all of the data.

The Hydroxide Ion Reaction. The large observed secondary isotope effects for the hydroxide ion catalyzed expulsion of chloroethanol and trifluoroethanol anions of 1.64 and 1.62, respectively, suggest a large amount of C–O bond cleavage in the transition states of these reactions. The corrected values correspond to 72–75% bond cleavage, as described in the Results and Table III. These results are consistent with the large negative value of $\beta_{lg} = -1.1$, which has been interpreted as evidence for a transition state with much (but not complete) C–O cleavage and incomplete solvation of the leaving alkoxide ion by water.[2]

These parameters show that the transition state for the hydroxide ion reaction has moved close to the lower right corner of Figure 3. The reaction involves cleavage of the hemiacetal anion with solvation of the leaving alkoxide ion by water (eq 22). A movement of the transition state to approximately this position when the weakly acidic water molecule is the "catalyst" is expected from the coefficients $p_{xy'} = \partial\beta_{lg}/-\partial pK_{HA} = 0.09$ and $p_{xy} = \partial\rho_n/-\partial pK_{HA} = 0.027$, which predict values of $\beta_{lg} = -1.1$ and $\gamma = 1 - \rho_n = 0.58 - 0.68$, respectively. However, water cannot act as a catalyst for concerted proton transfer because there is no thermodynamic advantage to proton transfer from water to the leaving alkoxide ion,[31] so that the shift in the transition state should be regarded as a change or "merging" of mechanisms.



There is an apparent inconsistency between the large amount of bond cleavage in the transition state, indicated by the values of $\beta_{lg} = -1.1$ and $\gamma = 0.72–0.75$, and the large ρ values for the addition of hydroxide and methoxide ions to substituted benzaldehydes, which have been interpreted in terms of a transition state that resembles the addition compound.[32] This difference can be accounted for by incomplete solvation of RO^- in the transition state, as mentioned above, by an analogous incomplete solvation of the negative charge on the carbonyl oxygen atom, and by an electrostatic effect resulting from the introduction into the transition state of a negative charge that is "seen" by substituents on the benzaldehyde.[2,32,33]

Summary. We conclude that general-acid–base catalysis of the expulsion and addition of alcohols and water occurs through a concerted reaction mechanism with an important component of proton transfer in a mobile transition state, **1**. It appears that the proton would rather be flying, or at least skating, than resting in a potential well.

The effects of polar substituents in the leaving group on the structure of the transition state can be summarized as shown in Scheme I. The numbers in this scheme represent very crude estimates of the "effective charges" and bond orders in the transition state for catalysis by acetic acid, as estimated from α, β_{lg},[2] and the secondary isotope effects reported here. We do not believe that these numbers are correct estimates of bond orders for a variety of reasons, including nonlinear relationships between different parameters for estimating bond orders,[19] but the data support the conclusion that the *changes* in the transition state with

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[29] Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 1113–1118.

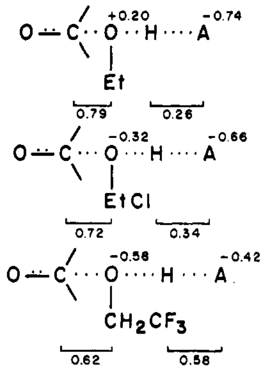
[30] Bernasconi, C. F.; Gandler, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 8117–8124.

[31] Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731–4732.

[32] Bell, R. P.; Sorensen, P. E. *J. Chem. Soc., Perkin Trans. 2*, **1976**, 1594–1598. Orora, M.; Cox, B. G.; Sorensen, P. E. *Ibid.* **1979**, 103–107.

[33] Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 3288–3294 and references cited therein.

Scheme I



changing reactant structure are in the indicated directions.

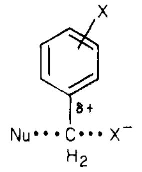
The reaction behaves as if the leaving group—not the proton—is in a well. As electron-withdrawing substituents are added that make the alcohol a better leaving group and a weaker base, there is *less* bonding to both the formaldehyde carbon atom and the proton in the transition state and a corresponding large increase in negative charge development on the leaving group. This is in the opposite direction from the behavior expected from a "Hammond effect" with respect to both C–O cleavage and proton transfer. The transition state adjusts itself to take advantage of the better leaving ability of the trifluoroethoxide anion; it adjusts to take advantage of the greater basicity of ethanol by utilizing more acid catalysts when the C–O bond becomes harder to break.

The proton shows the opposite behavior. It moves closer to the oxygen atom of ethanol, which develops positive charge in the transition state, than to that of trifluoroethanol, which develops negative charge in the transition state.[34] Thus, the proton transfer seems to drive, rather than follow, the reaction.

There appears to be a net expansion—or explosion—of the transition state as the leaving alcohol has less tendency to bond to carbon and to the proton (Scheme I). This seems to require a decrease in the total bond order in the transition state as the leaving group becomes less basic. It corresponds to a nonadditivity or imbalance of the amounts of bond formation and cleavage, as described above.

All of this makes sense if acid catalysis of this class of reactions is regarded as an electrophilic displacement reaction by the acid on oxygen, with formaldehyde as the leaving group, rather than as departure of a leaving group that is assisted by acid catalysis. Adding a proton to oxygen simply pulls electrons away from carbon and cleaves the C–O bond. In the reverse direction it can be regarded as an electrophilic attack of the carbonyl group on oxygen with displacement of the proton to a base rather than as nucleophilic attack of oxygen that is assisted by a base catalyst. In the direction of cleavage this is an A-S_E2 displacement. In this view the central oxygen atom is almost a passive participant, with the driving force for the reaction provided by the two electrophilic reagents. Electron-withdrawing substituents on the alcohol facilitate bond cleavage by helping to pull electrons away from the C–O and H–O bonds.

There is a close analogy of this situation to the behavior of the central carbon atom in nucleophilic displacement reactions. The central oxygen atom does what it is best fitted to do, accepting more negative charge upon addition of electron-withdrawing substituents, just as the central carbon atom of a benzyl halide undergoing nucleophilic displacement (**3**) develops more positive charge upon addition of electron-donating substituents.[33] With further stabilization of a cationic central carbon atom, as in reactions of methoxymethyl derivatives, the transition state for nucleophilic displacement approaches the structure of a carbenium ion.[35] With increasing stabilization of the ionized central atom there is less bond making and more bond breaking to this atom, and the transition state moves in an "anti-Hammond", perpendicular direction toward the anionic oxygen or cationic carbon intermediate. Thus, a weakly basic oxyanion interacts weakly with both the carbonyl group and the acid in the transition state. With still more stabilization of the charge on the central atom the reaction proceeds through an ionic intermediate in a fully stepwise mechanism, as in the uncatalyzed expulsion of stable anionic leaving groups or in classical carbenium ion reactions.



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[34] Ethanol is initially more basic than trifluoroethanol, so that the difference in basicity of the two leaving groups in the transition state will be smaller than suggested by the difference in β_{lg} or "effective charge". However, the effect of one charge on the p*K* of an alcohol is ~16 p*K* units, so that the difference in β_{lg} of >0.8 should represent a considerably larger change in basicity than the difference of 4 units in the p*K* of the two alcohols.

[35] Craze, G. A.; Kirby, A. J.; Osborne, R. *J. Chem. Soc., Perkin Trans. 2*, **1978**, 357–368. Knier, B.; Jencks, W. P. *J. Am. Chem. Soc.*, in press.