

Structure-Reactivity Coefficients for General Acid Catalysis of Semicarbazone Formation¹

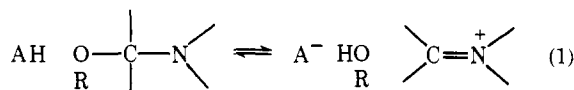
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Abstract: The Brønsted coefficient of $\alpha = 0.80 \pm 0.02$ for catalysis by phosphonate buffers of the dehydration step of semicarbazone formation from substituted benzaldehydes is independent of the substituent on the aldehyde. Conversely, the Hammett ρ of -1.9 is independent of acid strength and the interaction coefficient $\rho_{xy} = \partial\rho / -\partial pK_{HA} = \partial\alpha / \partial\sigma$ is indistinguishable from zero. The facts that (1) this class of reaction exhibits large interaction coefficients $\rho_{xy} = \partial\beta_{1g} / -\partial pK_{HA} = \partial\alpha / \partial pK_{1g}$ for substituents on the central atom and (2) α does not increase with acid strength ($\rho_x \geq 0$) mean that substituent effects involving central atoms can vary independently of those on end atoms. This corresponds to a shift of the coordinates for central atom effects (β_{1g}) on an energy diagram that is defined in terms of structure-reactivity coefficients for end atoms (α and ρ); i.e., a single three-dimensional diagram with fixed scales does not describe structure-reactivity interactions for both central and end atoms. The results may be accounted for by (1) a direct electrostatic interaction between polar substituents that does not require changes in bond length ("Hine effect") and (2) changes in the A-H...O-distance, so that a stronger acid and the leaving group can move together to give a "tighter" transition state, for example. The transition state is imbalanced, with a large amount of C-O cleavage but relatively little electron donation by resonance from the benzene ring or the nitrogen atom.

Introduction

The reversible addition of water and alcohols to electrophilic centers, such as iminium ions, frequently proceeds with general acid-base catalysis according to the class *n* mechanism² of eq 1.



There is strong evidence, principally from structure-reactivity behavior, that this mechanism is concerted for the cleavage of acetals and ortho esters and of addition compounds of a phthalimidium ion, imines, and formaldehyde.³⁻⁷ These reactions characteristically exhibit an increased Brønsted α value as the leaving alcohol becomes more basic and a complementary increased dependence on leaving group basicity, β_{1g} , as the catalyzing acid becomes stronger. The hydrolysis of substituted-benzaldehyde methyl phenyl acetals also exhibits an increase in ρ with stronger acid catalysts and a complementary increase in α with electron-withdrawing substituents on the benzaldehyde.³ This behavior is consistent with a more-or-less diagonal reaction coordinate on a three-dimensional energy diagram with separate axes for the proton transfer and C-O bond cleavage processes in these reactions.³⁻⁹

In order to examine the interrelationship between the effects of polar substituents on the catalyst and on the electrophilic reagent in the benzaldehyde-hydrazone series of addition compounds, we have examined the dehydration step of semicarbazone formation from substituted benzaldehydes. Evidence that this class of reactions proceeds through a concerted mechanism has been obtained previously for the closely related alcohol addition compounds of tosylhydrazones.⁵

Experimental Section

Materials. Organic reagents were redistilled, recrystallized, or sublimed before use. Potassium hydrogen dichloromethylphosphonate was prepared following the method of Kinnear and Perren,¹⁰ except that the phosphoryl dichloride was not isolated. The reaction mixture was cooled and added slowly to 108 g of ice, layer; the aqueous layer was adjusted to pH 11 with potassium hydroxide and filtered. The filtrate was then adjusted to pH 3 with sulfuric acid and filtered again; the filtrate was evaporated to dryness. Two recrystallizations from ethanol-water gave a product (mp 244–248 °C dec) with an equivalent weight of 207 (theoretical, 203) determined by titration with

potassium hydroxide. Ethylphosphonic acid was prepared by hydrolysis of the diethyl ester by refluxing in 8 M hydrochloric acid for 15 h. After solvent removal, a concentrated aqueous solution of the crude acid was neutralized to pH 5 with potassium hydroxide and evaporated to dryness. The crude monopotassium salt was recrystallized from methanol-ethanol. Trichloromethylphosphonic acid was converted to the monopotassium and dipotassium salts by neutralizing with potassium hydroxide to pH 3 and 8, respectively, followed by evaporation to dryness and recrystallization from ethanol-water. Chloromethylphosphonic acid was converted to the monopotassium salt by neutralization with potassium hydroxide to pH 3.4, followed by evaporation to dryness and recrystallization from ethanol-water. Glass-distilled water was used throughout.

Stock solutions of semicarbazide hydrochloride were stored in the cold and adjusted to the pH of the buffer immediately before use. Stock solutions of the aldehydes were prepared in acetonitrile and refrigerated.

Kinetics. Pseudo-first-order rate constants for the reactions of substituted benzaldehydes ($4\text{--}6 \times 10^{-5}$ M) with semicarbazide (usually 0.1 M) were determined spectrophotometrically at the absorption maximum of the semicarbazone product from plots of $\ln(A_\infty - A_t)$ against time. The reactions were initiated by the addition of 0.01 mL of a stock solution of the benzaldehyde in acetonitrile to 3 mL of reaction mixture. All runs, except those with *p*-nitrobenzaldehyde, were linear for at least 2 half-lives. Corrections for small changes in apparent pH ($\pm 0.05\text{--}0.15$) with changing buffer concentration were made according to

$$k_{\text{cor}} = k_{\text{obsd}} - k_0 \left(\frac{[\text{H}^+]_1 - [\text{H}^+]_2}{[\text{H}^+]_2} \right)$$

in which $[\text{H}^+]_1$ is for a given run, $[\text{H}^+]_2$ is for the run of lowest pH (usually at the lowest buffer concentration), and k_0 is the rate constant at zero buffer concentration. Experiments at pH values outside the range of buffering capacity of the catalyst were run in the presence of a constant concentration of a different buffer to maintain constant pH: 0.1 M cacodylate at pH 6 and 0.1 M ethyl phosphonate at pH 7. The ionic strength was maintained at 1.0 with potassium chloride. Several runs using potassium sulfate instead of potassium chloride did not give significantly different values of k_{obsd} . Rate constants for *p*-chlorobenzaldehyde hydrazone formation were determined in the same way, at 300 nm. Second-order rate constants, k_{HA} , for carbinolamine dehydration were calculated from the equation

$$k_{\text{HA}} = \frac{k_2}{f_{\text{HA}}} \left(\frac{1 + K_{\text{ad}}[\text{RNH}_2]}{K_{\text{ad}}[\text{RNH}_2]} \right) \quad (2)$$

in which k_2 is the slope of a plot of k_{cor} against buffer concentration, f_{HA} is the fraction of buffer present as free acid, K_{ad} is the equilibrium constant for carbinolamine formation, and $[\text{RNH}_2]$ is the concentration of semicarbazide or hydrazine free base. Plots of k_2 against f_{HA} indicate that there is no significant general base catalysis under

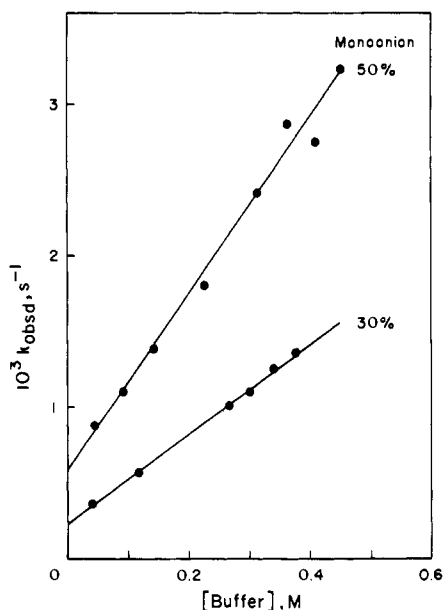


Figure 1. Dependence of the pseudo-first-order rate constants for benzaldehyde semicarbazone formation on the concentration of ethyl phosphonate buffers, 30 and 50% monoanion, at 25 °C and ionic strength 1.0 (KCl).

the conditions of these experiments. Second-order rate constants for catalysis by the proton were obtained in the same manner from plots of k_0 against $-\text{pH}$. The values of K_{ad} for semicarbazide were taken from measured values in 25% ethanol¹¹ and were corrected by the factor 0.75, the ratio of the values of K_{ad} for *p*-chlorobenzaldehyde in water and 25% ethanol;¹² K_{ad} for *p*-chlorobenzaldehyde and hydrazine¹² is 14 M⁻¹.

Experiments with *p*-nitrobenzaldehyde exhibited drift of the endpoint of ~4%, with a second, slow phase of the reaction that has approximately 8% of the rate constant of the initial reaction. Satisfactory first-order kinetics for the first phase were obtained using endpoints that were calculated by adding 3% of the observed absorbance change to the observed absorbance after 5 half-times. It is possible that the slow phase is a consequence of dehydration of the hydrate of *p*-nitrobenzaldehyde, which accounts for approximately 25% of the total concentration of *p*-nitrobenzaldehyde at equilibrium in water.¹³ No further correction for the slow phase was made because the same values of k_{obsd} were obtained with aldehyde that was added in anhydrous acetonitrile and from an equilibrated solution in water. Under the conditions of these experiments approximately 75% of the unhydrated *p*-nitrobenzaldehyde is immediately converted to the carbinolamine addition compound upon addition to the reaction mixtures.

Results

Typical experimental data for the determination of catalytic constants are shown in Figure 1. The second-order rate constants, k_{HA} , for general acid catalysis of the dehydration step in the formation of semicarbazones from a series of substituted benzaldehydes are given in Table I. Brønsted and Hammett plots, showing the effects on the rate of polar substituents in the acid and aldehyde, respectively, are shown in Figures 2 and 3, and the (least-squares) α and ρ^{H} coefficients are given in Table II. Statistical corrections were made according to Bell and Evans.¹⁴ Catalytic constants based on k_{obsd} rather than k_{cor} values do not give significantly different α values (Table II). Normalized values of ρ for the rate constants were calculated⁹ based on a value of $\rho = -2.1$ for the equilibrium constant, K_{eq} , of the dehydration reaction (Scheme I) and are also given in Table II. The value of $\rho_{\text{eq}} = -2.1$ was estimated from values of $\rho = -1.9$ for the protonation of substituted benzaldehyde oximes ($1/K_{\text{a}}$, Scheme I)¹⁵ and $\rho = -0.17$ for the equilibrium dehydration of carbinolamines to give benzaldehyde semicarbazones in 25% ethanol (K_{d} , Scheme I).¹¹

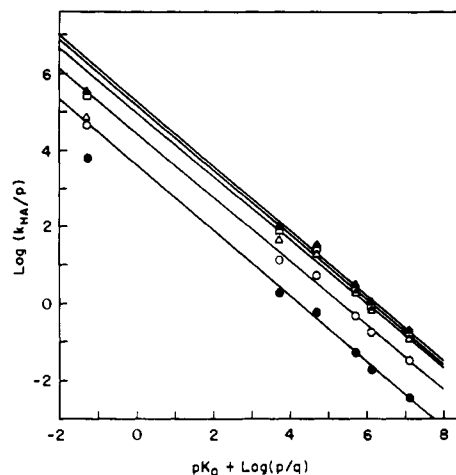


Figure 2. Brønsted plots for general acid catalysis of carbinolamine dehydration in the reaction of semicarbazide with *p*-nitrobenzaldehyde (●), *p*-chlorobenzaldehyde (○), benzaldehyde (Δ), *p*-methylbenzaldehyde (▲), and *p*-methoxybenzaldehyde (□).

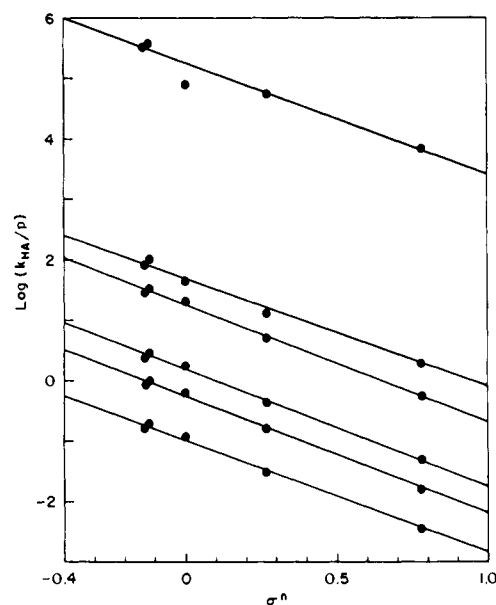
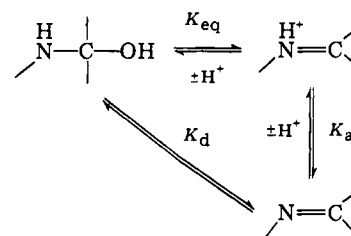


Figure 3. Hammett plots based on σ^{ρ} for the dehydration step of semicarbazone formation from substituted benzaldehydes. The acid catalysts are listed in Table II.

Scheme I



Rate constants for general acid catalysis of the dehydration step of hydrazone formation from *p*-chlorobenzaldehyde are given in Table III. The rate constants for catalysis by phosphonates give a (least-squares) Brønsted slope of $\alpha = 0.81$, which is not significantly different from the slope of $\alpha = 0.80$ that was observed for semicarbazone formation from *p*-chlorobenzaldehyde. These results differ from previously reported values of $\alpha = 0.72$ and 0.62 for the dehydration steps of semicarbazone and hydrazone formation, respectively, which were based on catalytic constants for different types of cata-

Table I. General Acid Catalysis of the Dehydration Step of Semicarbazone Formation from Substituted Benzaldehydes^a

catalyst, XPO ₃ H ⁻	fraction acid	k_2 , M ⁻¹ s ⁻¹	k_{HA} , M ⁻¹ s ⁻¹
<i>p</i> -O ₂ NC ₆ H ₄ CHO			
CCl ₃	0.00138	1.89 × 10 ⁻³	1.91
	0.0187	2.81 × 10 ⁻²	
CHCl ₂	0.048	1.85 × 10 ⁻²	0.556
	0.0050	2.25 × 10 ⁻³	
CH ₂ Cl	0.071	3.96 × 10 ⁻³	0.0682
	0.36	1.66 × 10 ⁻²	
OH	0.30	3.78 × 10 ⁻³	0.0163
	0.50	7.50 × 10 ⁻³	
C ₂ H ₅	0.30	7.25 × 10 ⁻⁴	0.00347
	0.50	1.40 × 10 ⁻³	
(H ⁺)			6.6 × 10 ³
<i>p</i> -ClC ₆ H ₄ CHO			
CCl ₃	0.00138	4.33 × 10 ⁻³	13.4
	0.0187	5.70 × 10 ⁻²	
CHCl ₂	0.048	5.08 × 10 ⁻²	5.15
	0.0050	6.83 × 10 ⁻³	
CH ₂ Cl	0.071	1.07 × 10 ⁻²	0.602
	0.36	4.72 × 10 ⁻²	
HO	0.30	1.11 × 10 ⁻²	0.161
	0.50	1.94 × 10 ⁻²	
C ₂ H ₅	0.30	1.96 × 10 ⁻³	0.031
	0.50	4.06 × 10 ⁻³	
(H ⁺)			5.07 × 10 ⁴
C ₆ H ₅ CHO			
CCl ₃	0.0179	4.80 × 10 ⁻²	45.1
	0.00138	7.50 × 10 ⁻³	
CHCl ₂	0.048	7.77 × 10 ⁻²	19.8
	0.005	9.7 × 10 ⁻³	
CH ₂ Cl	0.071	1.65 × 10 ⁻²	2.37
	0.36	6.83 × 10 ⁻²	
HO	0.30	1.72 × 10 ⁻²	0.622
	0.50	2.74 × 10 ⁻²	
C ₂ H ₅	0.30	2.98 × 10 ⁻³	0.119
	0.50	5.74 × 10 ⁻³	
(H ⁺)			7.3 × 10 ⁴
<i>p</i> -CH ₃ C ₆ H ₄ CHO			
CCl ₃	0.0187	1.66 × 10 ⁻²	100
	0.00138	7.15 × 10 ⁻³	
CHCl ₂	0.048	5.87 × 10 ⁻²	31.9
	0.005	7.93 × 10 ⁻³	
CH ₂ Cl	0.071	1.28 × 10 ⁻²	3.96
	0.36	5.95 × 10 ⁻²	
HO	0.30	1.25 × 10 ⁻²	0.99
	0.50	2.30 × 10 ⁻²	
C ₂ H ₅	0.30	2.41 × 10 ⁻²	0.20
	0.50	4.68 × 10 ⁻³	
(H ⁺)			3.62 × 10 ⁵
<i>p</i> -CH ₃₀ C ₆ H ₄ CHO			
CCl ₃	0.0187	2.52 × 10 ⁻²	83.3
	0.0019	4.28 × 10 ⁻³	
CHCl ₂	0.048	3.02 × 10 ⁻²	29.1
	0.005	3.93 × 10 ⁻³	
CH ₂ Cl	0.071	6.04 × 10 ⁻³	3.31
	0.36	2.71 × 10 ⁻²	
HO	0.30	5.80 × 10 ⁻³	0.84
	0.50	1.09 × 10 ⁻²	
C ₂ H ₅	0.30	1.09 × 10 ⁻³	0.17
	0.50	2.30 × 10 ⁻²	
(H ⁺)			2.99 × 10 ⁵

^a Determined at 25 °C, ionic strength = 1.0 (KCl), in the presence of 0.1 M semicarbazide.

lysts, including the proton.¹² The difference results from the inclusion of the catalytic constant for the proton in the previously reported Brønsted correlation and from a positive deviation of the rate constants for weakly acidic protonated ter-

Table II. Structure-Reactivity Correlations for the Dehydration Step of Benzaldehyde Semicarbazone Formation

catalyst	pK _a	ρ ^a	ρ _{norm} ^b
hydronium ion	-1.74	-1.83	-0.87
trichloromethylphosphonate	4.28 ^c	-1.78	-0.85
dichloromethylphosphonate	4.97 ^c	-1.93	-0.92
chloromethylphosphonate	5.95 ^d	-1.94	-0.92
phosphate	6.46 ^e	-1.91	-0.91
ethylphosphonate	7.60 ^c	-1.84	-0.88
benzaldehyde	σ _n ^f	Brønsted α	
<i>p</i> -NO ₂	0.778	0.82	0.80 ^g
<i>p</i> -Cl	0.26	0.80	
H	0	0.78	
<i>p</i> -CH ₃	-0.12	0.81	0.82 ^g
<i>p</i> -OCH ₃	-0.13	0.81	

^a Based on values of σ_n.¹⁷ ^b Normalized, based on a value of ρ_{eq} = -2.1 (see text). ^c Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637. ^d Determined by titration. ^e Reference 5. ^f Reference 17. ^g Based on *k*_{obsd} rather than *k*_{cor}.

Table III. Acid Catalysis of the Dehydration Step of *p*-Chlorobenzaldehyde Hydrazone Formation^a

catalyst	fraction acid	k_2 , M ⁻¹ s ⁻¹	k_{HA} , M ⁻¹ s ⁻¹
trichloromethylphosphonate	0.0099	3.7 × 10 ⁻²	939
	0.0013	3.17 × 10 ⁻²	
dichloromethylphosphonate	0.005	3.35 × 10 ⁻²	172
chloromethylphosphonate	0.045	3.46 × 10 ⁻²	22.8
	0.065	3.8 × 10 ⁻²	
ethylphosphonate	0.30	5.07 × 10 ⁻²	1.85
	0.72	4.2 × 10 ⁻²	
	0.95	2.77 × 10 ⁻²	
hydronium ion			5.49 × 10 ⁶

^a Determined at 25 °C, ionic strength 1.0 (KCl), in the presence of 0.05 M total hydrazine.

tiary amine catalysts above the Brønsted line for the phosphonate catalysts in the hydrazine reaction. The earlier conclusion that α decreases with increasing pK of the amine in this class of reaction¹² is, therefore, uncertain.

The rate constants obtained by Capon and Nimmo for the hydrolysis of substituted-benzaldehyde methyl phenyl acetals³ were found to give an optimal fit to linear Hammett plots using a Yukawa parameter^{16,17} of *r*⁺ = 0.5, to correct for electron donation by resonance in the transition state. The (least-squares) values of ρ range from -1.94 to -2.08 to -2.79 for catalysis by the proton, chloroacetic acid and pivalic acid, respectively. Plots of α against σ⁺ + 0.5Δσ_R⁺ and of ρ against pK_{HA} for the carboxylic acid catalysts were found to give slopes of 0.32 and -0.26, respectively. Normalization, based on a ρ value of -3.6 for the equilibrium formation of oxocarbenium ions from substituted acetophenone ketals,¹⁸ gives an average value for the coefficient *p*_{xy} = ∂α/∂σ = ∂ρ/∂pK_{HA} of ~0.081. Rate constants for the hydrolysis of benzaldehyde methyl substituted-phenyl acetals³ were found to give slopes of 0.22 for α against pK_{1g} and -0.17 for β_{1g} against pK_{HA}, from which *p*_{xy}' = ∂α/∂pK_{1g} = ∂β_{1g}/∂pK_{HA} was taken to be 0.2.

Discussion

The general acid-catalyzed cleavage of addition compounds of water and alcohols with benzaldehyde hydrazones (eq 1) is one example of the class of reactions in which acids catalyze the expulsion of HOR from electrophilic centers by a reaction mechanism that appears to be concerted.³⁻⁷ Many of the properties of these reactions can be conveniently illustrated with three-dimensional reaction coordinate-energy diagrams

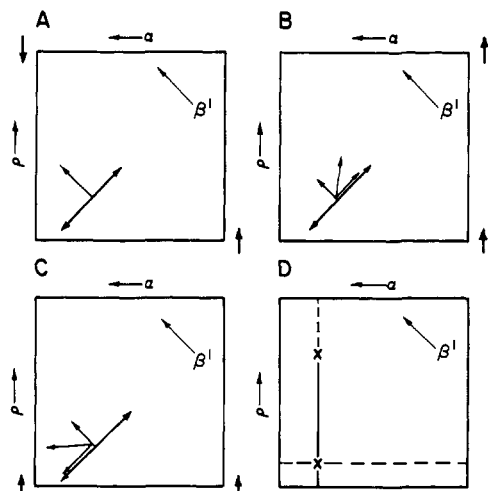


Figure 5. Reaction coordinate diagrams, defined as in Figure 4, showing changes in the position of the transition state with changing substituents on the reactants and catalysts. (A) The effect of an electron-donating substituent on the alcohol that lowers the energy of the upper left corner and raises the energy of the lower right corner. (B) Effect of an electron-withdrawing substituent that increases the strength of the acid and the energy of the right side of the diagram. Shifts perpendicular and parallel to the reaction coordinate give a resultant shift of the transition state that is close to vertical. (C) Effect of an electron-withdrawing substituent in the benzaldehyde that increases the energy of the electrophilic reagent and the lower part of the diagram. (D) The intersection of the dashed lines shows the constant position of the transition state with increasing acid strength on the scales defined by α and ρ ; the crosses show the large shift in the position of the transition state on the β' scale with increasing acid strength.

stants for the proton and trichloromethylphosphonate monoanion in Figure 2 may possibly have the same explanation. The amount and direction of small changes of this kind in the position of the transition state are determined by the curvatures and orientation of the energy surface in the region of the saddle point which, in turn, may be calculated for a given reaction from the observed structure-reactivity coefficients, such as those defined in eq 3-5.⁹

It is difficult or impossible to explain results of this kind in terms of simple "Hammond" or "anti-Hammond" effects based on two-dimensional reaction coordinate-energy curves. For example, the increase in β_{1g} with decreasing pK of the acid (eq 3) might be regarded as an anti-Hammond effect that could be accounted for by a proton that is in a potential well at the transition state. Thornton has described Hammond and anti-Hammond effects in terms of perturbations of parabolic energy maxima or minima that are parallel or perpendicular to the reaction coordinate, respectively.²¹ Considering only the perpendicular, anti-Hammond effect, the increase in β_{1g} could reflect a change in the position of the potential well minimum for the proton by the amount X as the energy of the acid is increased by an amount m , according to the relationship $X_{ex} = -m/k$, in which k is the force constant of the parabola. However, this perturbation and shift in the position of the well correspond to an equal increase in α with increasing acid strength, which is not observed. The observed increase in α with increasing base strength, but not increasing acid strength, can be explained by the geometry of the energy surface only if the orientation and curvature of the saddle point are taken into account, as in Figures 4 and 5, so that shifts in the position of the transition state are the resultant of perturbations both perpendicular and parallel to the reaction coordinate.

The shift in the position of the transition state toward the top of the diagram with increasing acid strength (Figure 5B) corresponds to an increased (less negative) ρ , as well as to an increase in β_{1g} , if all of the structure-reactivity interactions

can be described by a single diagram with common scales. This change corresponds to an earlier transition state for C-O bond cleavage, as described by a positive coefficient

$$p_{xy} = \partial \rho / -\partial p K_{HA} = \partial \alpha / \partial \sigma \quad (6)$$

A positive p_{xy} coefficient also requires that an electron-withdrawing substituent on the benzene ring (increased σ) that increases the energy of the cationic center at the bottom of the diagram will shift the position of the transition state to the left with an increase in α , as shown in Figure 5C. Such changes have been observed for the cleavage of benzaldehyde methyl aryl acetals³ and correspond to a value of $p_{xy} = 0.08$ (see Results section).

The experiments described here were carried out to determine whether a change in the position of the transition state corresponding to a positive p_{xy} coefficient can also be detected in the carbinolamine system. The results (Figures 2 and 3 and Table II) show that both α and $-\rho$ are large and constant. The value of $\alpha = 0.80 \pm 0.02$ corresponds to a large amount of proton transfer and the normalized ρ value of -0.89 ± 0.04 , based on $\rho = -1.87 \pm 0.09$ and an estimated ρ_{eq} value of -2.1 , corresponds to a large amount of C-O bond cleavage in the transition state. There is no indication of either the increase in ρ with increasing acid strength nor the increase in α with electron-withdrawing substituents on the benzaldehyde that would be expected for shifts of the transition state upward or to the left; i.e., the p_{xy} coefficient of eq 4 is indistinguishable from zero. There is also no indication of a change in α with changing σ in plots of the rate constant ratios, $\log(k_H/k_X)$, for the different benzaldehydes with substituents X; we believe that a change in slope corresponding to $p_{xy} = 0.02$ would have been observed if it existed. Sayer and DePecol have reached a similar conclusion from the observation that the Brønsted coefficient for the hydrolysis of 1,3-dimethyl-5-(*p*-tolylimino)barbituric acid is essentially the same as for carbinolamine reactions of benzaldehyde derivatives that have much less electron-withdrawing substituents on the carbon atom.²²

If the α , β' , and ρ coefficients can be represented by the horizontal, diagonal, and vertical coordinates, respectively, on a single square diagram, such as Figure 4, or on a transformed diagram in which the $\beta' = y'$ coordinate is vertical,⁹ then the relationship between the $p_{xy'}$, p_{xy} , and p_x coefficients is given⁹ by

$$p_{xy'} = p_{xy} - p_x \quad (7)$$

This relationship is a quantitative statement of the qualitative expectation described above, that ρ as well as β_{1g} should increase if the position of the transition state shifts upward with increasing strength of the catalyzing acid (Figure 5B); however, it shows that the relationship also depends on the Hammond coefficient p_x (eq 4). The experimental fact that $p_x \geq 0$ means that p_{xy} should be at least as large as $p_{xy'}$. Since $p_{xy'} = 0.07$ is large and easily detectable, the experimental result that p_{xy} is indistinguishable from zero requires the conclusion that the relationship of eq 7 does not hold and that *the three structure-reactivity parameters cannot be described quantitatively by a single structure-reactivity diagram with constant scales for the three parameters*. The same conclusion is required by the structure-reactivity coefficients for the hydrolysis of benzaldehyde methyl aryl acetals. Although the rate constants for this reaction³ give a positive p_{xy} coefficient of 0.08, this coefficient is much smaller than the value of $p_{xy} \geq 0.2$ that is required by eq 7 and by the values of $p_{xy'} = 0.2$ and $p_x \geq 0$.⁹ A similar imbalance has recently been observed for the acid-catalyzed expulsion of alcohols from Meisenheimer complexes.²³

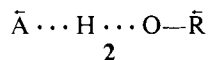
These results show that substituent effects on end atoms can be described by a diagram that is defined in terms of the structure-reactivity parameters α and ρ , and that substituent

effects on a central atom and one end atom may be described by a different diagram, defined in terms of α and β_{1g} , for example, but a single diagram does not describe all three parameters unless an additional dimension is added to permit two of the parameters to vary independently of the third. In other words, the data require that certain changes in structure-reactivity coefficients involving central atoms can take place independently of those involving end atoms.

These changes are large and well beyond the borderline of experimental detection. The $p_{xy'}$ coefficient of 0.07 corresponds to an increase in β_{1g} of 0.56 unit as the catalyst is changed from ethylphosphonate monoanion to the proton, and the observed β_{1g} values, based on $\log(k_{HA}/k_{HOAc})$ from the earlier data,⁵ increase from -0.09 to $+0.48$ as the acid strength increases over this range. Such a shift is shown by the crosses in Figure 5D. The amount of C-O bond cleavage is also measured by the vertical scale on the diagram so that a large increase in ρ would also be expected if all the parameters were described by a single diagram. The (normalized) change in ρ is expected to be smaller than the change in β_{1g} (because protonation of the carbinolamine will be aided by electron-donating substituents, with a ρ value of about -1.0^{24}) but should be easily detectable for such a large shift in the position of the transition state. The position of the transition state, as defined by the α and ρ scales, does not move by a detectable amount from the position shown by the intersecting lines in Figure 5D. This requires that if the diagram is defined in terms of α and ρ , the scale for β_{1g} at the observed α value must move downward as the acid strength is increased. Conversely, if the diagram is defined in terms of α and β_{1g} the increase in β_{1g} requires a corresponding upward shift of the scale for ρ with increasing acid strength.

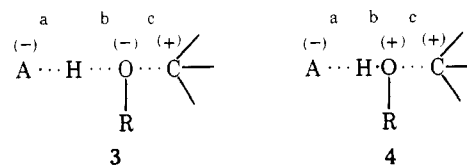
We propose two explanations for this result.

(1) The observed behavior corresponds to an electrostatic "Hine effect" that can cause changes in structure-reactivity coefficients without changes in bond lengths.^{9,25} Consider, for example, the effect of polar substituents on the stability of **2**, with the position of the proton held constant. An electron-withdrawing substituent that increases the acidity of AH will be stabilized by an electron-donating substituent in the alcohol through a simple electrostatic interaction and will thereby stabilize the transition state relative to the separated reactants and increase β_{1g} . Since this electrostatic interaction depends only on the distance between the interacting substituents, and not on the position of the proton, it will cause a shift in the scale for β_{1g} to larger values as the strength of the acid is increased (for example) over the entire diagram.⁹ Although this electrostatic effect undoubtedly contributes to the observed $p_{xy'}$ coefficients, it is unlikely that the contribution of $\tau = p_{xy'}$ (electrostatic) is much larger than the value of 0.024 originally suggested by Hine^{25,26} so that another explanation is required for the greater part of the observed $p_{xy'}$ coefficients in the range 0.07 to 0.2.



(2) The observed structure-reactivity interactions may be described by changes in the H-O distance that are not necessarily accompanied by changes in other bond lengths in the transition state. The transition state for catalysis of this class of reactions by a weak acid may be described by **3**. The large observed α means that there is much A-H bond cleavage (a), the large $-\rho$ value means that there is much C-O bond cleavage (c), and the negative β_{1g} value means that the amount of proton transfer is insufficient to overcome the development of negative charge on the leaving oxygen atom that results from cleavage of the C-O bond in the transition state (b). For a stronger acid the constant α and ρ values indicate no detectable change in the A-H and C-O bond lengths, a and c (if anything,

α and the A-H bond length decrease), but the fact that β_{1g} becomes positive or less negative shows that proton transfer is largely or entirely overcoming the negative charge devel-



opment from C-O bond cleavage. This larger influence of proton transfer on the alcohol is consistent with a shortening of the H-O bond (b) and corresponds to an overall tightening of the transition state (**4**). An increase in the basicity of the leaving alcohol can also shorten the H-O bond length (b) by moving the oxygen atom toward the proton, as suggested by the increased β_{1g} with increasing pK_{ROH} (negative $\partial\beta_{1g}/-\partial pK_{1g} = p_{y'}$), and increases α , as is required by the mathematical relationship of eq 1.

Eliason and Kreevoy have independently suggested, on theoretical grounds, that the position of A-H may shift relative to that of OR in the transition state without changes in the Brønsted α value.²⁷ This corresponds to a tightening or loosening of the transition state similar to that shown in **3** and **4**.

These changes may be rationalized qualitatively in terms of the geometry of the energy diagrams. With a predominantly diagonal reaction coordinate the leaving oxygen atom is in a broad potential well with respect to movement perpendicular to the reaction coordinate and toward the corners of the diagram, so that it can move toward the proton of a relatively strong acid, for example, to give an "anti-Hammond" effect. However, the position of the proton relative to A^- remains relatively constant with changing acid strength because it is "in flight," not in a well, and the Hammond effect overcomes any tendency for it to move toward the alcohol. When the basicity of the leaving alcohol is increased, the transition state shifts diagonally, perpendicular to the reaction coordinate, and gives an increase in α and β_{1g} , as described above (Figure 5A). It is not yet known whether ρ and the C-O bond length change in an analogous manner with changing substituents on the central oxygen atom of the alcohol (this corresponds to a $p_{yy'}$ interaction coefficient of the diagrams⁹).

These results correspond to still another example of *imbalance* of the extent to which different processes have occurred in the transition state and to a nonadditivity of the "effective charges" on reacting atoms that may be used to describe polar substituent effects.^{5,28,29} Curvature of the diagonal lines of constant $\beta' = y'$ in the diagrams can account for the anomalous position of a single β' value⁹ and must exist in a diagram that is defined in terms of α and ρ , but it does not account for the large change in β' when α and ρ remain essentially constant. A water molecule between the acid and alcohol that can act as an intermediate proton acceptor could account for the anomalous combination of $\alpha = 0.75$, $\rho = -2.8$, and $\beta_{1g} = -0.58$, for cleavage of benzaldehyde methyl aryl acetals, which gives a transition state that falls below the lower edge of a diagram analogous to Figure 4,⁹ but it does not account for the imbalance of the values of $\alpha = 0.8$, $\rho_n = -0.9$, and $\beta_{1g} = +0.4$ for catalysis by the proton of alcohol expulsion in the $ArCH(NHR)OR'$ system, which represents a deviation in the opposite direction. It is likely that interaction coefficients, such as p_{xy} and $p_{xy'}$, will themselves change if there are large shifts in the position of the transition state or if the position of the transition state approaches the edge of the diagram. Such changes correspond to third derivatives of $\log k$ with respect to substituent constants and will be difficult to measure quantitatively. The small observed p_{xy} coefficients

show that there are not large changes in the position of the transition state on the diagram that is defined by α and ρ .

Other Properties of the Transition State. In spite of the large amount of C-O bond cleavage, there is little or no electron donation by resonance from substituents on the benzaldehyde to the central carbon atom in the transition state. The ρ value of -1.9 for $\log k$ (Table II) is almost as large as the value of approximately -2.1 for the equilibrium constant of the overall reaction, but the excellent correlation with σ^+ for the rate constants (Figure 3) means that there has been very little electron donation by resonance in the transition state. Similarly, the α secondary deuterium isotope effects for the dehydration of benzaldehyde carbinolamines suggest that there has been little rehybridization toward the sp^2 carbon atom of the resonance-stabilized product in the transition state.³⁰ In contrast, there is a large amount of resonance stabilization of the immediate product, as shown by the facts that the equilibrium constants, K_H , for protonation of substituted benzylidene-1,1-dimethylethylamines³¹ ($1/K_a$, Scheme I) give a better correlation with ρ^+ than with ρ and the equilibrium constants for protonation of substituted benzaldehyde oximes¹⁵ may be correlated according to a modified Yukawa treatment^{16,18} to give $\rho = -1.55$, $\rho' = -1.07$, and $r^+ = 0.69$. Thus, there is an imbalance between the large amount of C-O cleavage, as measured by the effects of polar substituents, and the small amount of electron donation by resonance to the developing iminium ion in the transition state for C-O bond cleavage.

The rate constants for the acid-catalyzed dehydration step in the formation of a series of benzaldehyde hydrazones have a relatively small dependence on the basicity of the hydrazine moiety, with a value of $\beta_N = 0.4$.¹² Since replacement of the N-H proton of the carbinolamine by a methyl group has no significant effect on the rate of acid-catalyzed dehydration,³² there is no cleavage of this N-H bond in the transition state and there is a full positive charge on the nitrogen atom of the immediate product of the reaction (eq 1). The small value of β_N therefore means that there has been relatively little electron donation from nitrogen to form the double bond to carbon in the transition state. The small β_N and the large negative value of ρ for the rate constants suggest that electron donation from nitrogen lags behind C-O bond cleavage. A similar, but larger, imbalance in the transition state has been observed for the base-catalyzed dehydration step.⁵

We are left with a picture of the transition state in which there is a large amount of proton transfer and C-O cleavage, a variable structure with respect to polar substituent effects involving the central oxygen atom, a much smaller variation in structure with respect to the end atoms, and a relatively small amount of electron donation by resonance from both the nitrogen atom and the benzene ring.

References and Notes

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- (26) The magnitude of the electrostatic contribution to ρ_{xy} is given by the coefficient τ , as described by Hine.²⁵

$$\log K_{AB} = \tau(pK_{HA} - pK_{HOH})(pK_{HO}^0 + - pK_{BH}) - 1.74$$

There are several reasons for believing that this coefficient is not significantly larger than the value of 0.024 that was suggested by Hine. (1) The value of $\tau = 0.024$ gives a value of $K = 1.3 M^{-1}$ for the formation of a hydrogen-bonded complex of an acid of $pK = 8$ and its conjugate base that is consistent with the known marginal stability of such complexes in water; larger values would predict the formation of stable complexes, which are not observed.²⁵ Similarly, the calculated associated constant for a formic acid-formate complex of $0.6 M^{-1}$ is somewhat larger than a recent experimental value of $0.25 M^{-1}$ (Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 6221-6230). (2) A value of $\alpha = 0.2$ for the formation of hydrogen-bonded complexes between a series of acids and a constant base, with $pK_{BH^+} = 7$, gives a value of $\tau = 0.023$. These coefficients are related by $\alpha = -\tau(pK_{H_3O^+} - pK_{BH^+})$. It is unlikely that α is several times larger than 0.2 for the formation of a double potential well hydrogen bond, as would be required if τ were $\gg 0.024$. (3) Hine has set an absolute upper limit of $\tau < 0.057$ in water.²⁵ If this number were exceeded, the concentration of the hydrogen-bonded pair $HO^- \cdot H_3O^+$ would be larger than the concentration of H_2O in liquid water (personal communication from J. Hine). (4) The value of τ may be estimated directly to be approximately 0.013 as follows. Changes in the equilibrium constants for

$$AH + XCH_2Z \xrightleftharpoons{K_{AB}} AH \cdot XCH_2Z$$

$$\begin{array}{ccc} \parallel K_a & & \parallel K_a' \\ AH + XCH_2ZH' & \xrightleftharpoons{K_{AB}'} & AH \cdot XCH_2ZH' \end{array}$$

are related by

$$\Delta(pK_a - pK_a') = \Delta(\log K_{AB} - \log K_{AB}')$$

Assuming an attenuation factor of 0.5 per atom for the transmission of polar substituent effects, a change in the pK of AH will change pK_a' according to $\Delta pK_a' = 0.063 \Delta pK_{AH} = -\Delta(pK_a - pK_a')$ (the attenuation factor for the hydrogen atom is taken to be the same as for other atoms; the bond lengths for hydrogen bonds and other bonds suggest that this does not introduce a large error into the estimation). The development of a positive charge on Z is expected to decrease the basicity of the X atom of XCH_2Z by approximately 4.7 units (Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 5637-5649; Fox, J. P.; Jencks, W. P. *ibid.*, **1974**, *96*, 1436-1449). Taking XCH_2Z as the base, B, this shows that

$$\Delta(\log K_{AB} - \log K_{AB}') / \Delta pK_{AH} = 0.063$$

for a 4.7 unit change in pK_{BH} or 0.013 for a one unit change of pK_{BH} . Writing the Hine equation in the form of its second derivative

$$\partial(\Delta \log K_{AB} / \Delta pK_{AH}) / \partial pK_{BH} = \tau = 0.013$$

shows that this quantity is τ , the change in the dependence of $\log K_{AB}$ on pK_{AH} for a given change in the pK of BH. This estimation of τ is not exact, because of uncertainties in the attenuation factor, but it is probably correct to within a factor of 2 and is consistent with Hine's estimate of $\tau = 0.024$.
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