

There is available a set of compounds, which varies in basicity by four powers of ten, and are of similar structure. For many of these compounds the basicities have also been measured by the usual Hammett acidity scale in sulfuric acid; there are therefore several independent checks on the quality of the correlation. In this fashion it has been possible to determine the pK_{BH^+} for several *cis*-chalcones, most of which undergo isomerization far too rapidly^{13b} in moderately concentrated sulfuric acid for the Hammett procedure to be used.

It is to be noted (Table VI) that the *cis*-chalcones are uniformly less basic than the corresponding

trans-chalcones. The average decrease in basicity is a factor of 5.

pK of *trans*-4-Fluorochalcone.—The basicity of 4-fluorochalcone was measured by the hydrogen bonding method, and a value of $pK_{BH^+} = -5.22$ obtained. An independent check of this value by the method of Fox, Levins and Taft,⁴⁴ the F¹⁹ nuclear magnetic resonance shift, was very kindly carried out by Professor Taft. The value by this procedure is $pK = -5.10$.⁴⁵

(44) I. R. Fox, P. L. Levins and R. W. Taft, Jr., *Tetrahedron Letters*, No. 7, 249 (1961).

(45) R. W. Taft, Jr., personal communication.

[CONTRIBUTION No. 179 FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

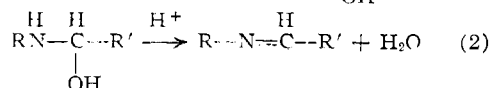
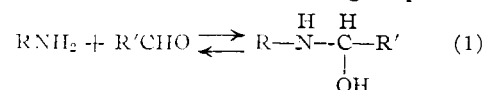
General Acid Catalysis of Semicarbazone Formation¹

BY E. H. CORDES AND W. P. JENCKS

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General acid catalysis of the attack of semicarbazide on a series of substituted benzaldehydes has been studied in aqueous solution at 25°. Protonated aldehydes do not appear to be intermediates in benzaldehyde semicarbazone formation, because the calculated rate constant for a reaction involving protonated *p*-nitrobenzaldehyde is larger than that for a diffusion-controlled reaction. From this and other arguments, based on the rates of proton transfer reactions, it is concluded that the general acid-catalyzed reaction involves concerted semicarbazide attack and proton transfer to the carbonyl group. The deuterium isotope effect on the catalytic constant for the hydrated proton is $k_H/k_D = 1.2$ and that for acetic acid is 1.6. The catalytic rate constants for chloroacetic acid, acetic acid and water are better correlated by σ^+ than by σ -substituent constants. Values of ρ^+ for these catalysts and the hydrated proton increase slightly with decreasing acid strength, from 0.71 for the hydrated proton to 0.94 for water. The Brønsted α -value was determined from the catalytic constants of several carboxylic acids and the hydrated proton for *p*-nitro-, *p*-chloro- and *p*-hydroxybenzaldehydes and acetophenone. Values of α near 0.25 were obtained in each case, indicating that α is insensitive to a moderate change in substrate reactivity. Relationships between the Brønsted α -value, the reactivity of the substrate and the reactivity of the nucleophilic reagent from the Hammett, Brønsted and Swain-Scott equations are discussed. In the case of *p*-chlorobenzaldehyde, the Brønsted plot was extended to include catalytic constants for thirty acids of varying structure and charge type.

Several investigations have established that the reaction of semicarbazide with aldehydes and ketones is subject to general acid catalysis.² Subsequent work has shown that, at neutral *pH*, the acid-catalyzed dehydration of the carbinolamine addition product (eq. 2) is the rate-determining step in semicarbazone formation, while under more acidic conditions the rate-determining step under-



goes a transition to rate-determining semicarbazide attack^{3,4} (eq. 1). The attack of semicarbazide on the carbonyl carbon atom obeys the rate law of eq. 3. Thus this reaction exhibits catalysis by general acids, the solvated proton and solvent.

$$r = \left[k_0 + k_H(H^+) + \sum_i k_{A_i}[A_i] \right] [RNH_2] [C=O] \quad (3)$$

(1) Supported by grants from the National Cancer Institute of the National Institutes of Health (C-3975) and the National Science Foundation. This investigation was carried out by E. C. during the tenure of a Predoctoral Fellowship from the National Heart Institute, U. S. Public Health Service.

(2) (a) J. B. Conant and P. D. Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932); (b) F. H. Westheimer, *ibid.*, **56**, 1962 (1934); (c) G. H. Stempel, Jr., and G. S. Schaffel, *ibid.*, **66**, 1158 (1944).

(3) W. P. Jencks, *ibid.*, **81**, 475 (1959).

(4) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

Several aspects of the general acid-catalyzed attack of nucleophilic reagents on the carbonyl carbon atom, including the mechanism of the catalysis, the variation in susceptibility to general acid catalysis as a function of the reactivity of substrate and nucleophilic reagent, and the relationship of catalyst structure to catalytic efficiency are of particular chemical and biochemical interest. This work was undertaken in an attempt to obtain information pertinent to these questions.

Experimental

Materials.—All carbonyl compounds were either redistilled under nitrogen or twice recrystallized before use. Solutions of carbonyl compounds were prepared in water containing approximately 15% ethanol and 10⁻⁴ M ethylenediaminetetraacetic acid and were stored at 2°. These solutions are stable for several days under these conditions. Semicarbazide hydrochloride was recrystallized at least twice from aqueous ethanol and solutions were prepared just prior to use. Trimethylamine-N-oxide (m.p. 95–96°), N,N-dimethylhydroxylamine (m.p. 106°) and glycine hydroxamic acid (m.p. 141–143°) were prepared by known methods.^{5–7} Formohydroxamic acid (m.p. 74–76°) and acetohydroxamic acid (m.p. 89.5–92°) were prepared by slight modifications of the method employed for the preparation of glycine hydroxamic acid.⁷ Other reagents, except for reagent grade inorganic salts, were recrystallized or redistilled before use. Solutions of all nitrogen bases were prepared just prior to use. Deuterium oxide (>99%) was redistilled before use. Glass-distilled water was used throughout.

(5) W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **75**, 1004 (1899).

(6) H. Hepworth, *ibid.*, **119**, 251 (1921).

(7) S. R. Safir and J. H. Williams, *J. Org. Chem.*, **17**, 1298 (1952).

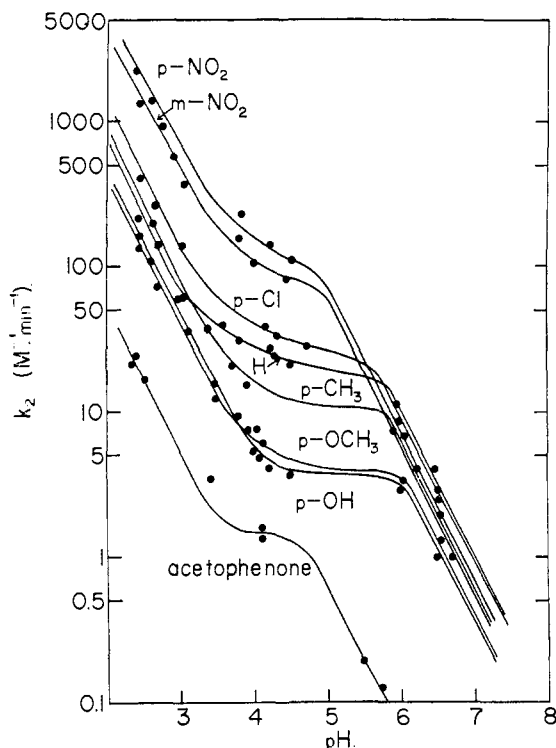


Fig. 1.—Logarithm of second-order rate constants, based on the concentration of the free base of semicarbazide, for semicarbazone formation from a series of substituted benzaldehydes and acetophenone at 25°. All rate constants have been extrapolated to zero buffer concentration; ionic strength = 0.50 (for acetophenone experiments ionic strength = 1.0).

Ultraviolet measurements were made on a Zeiss PMQ II spectrophotometer.

Kinetic measurements were carried out spectrophotometrically at 25° as previously described.^{3,4} Catalytic constants were obtained from the slopes of second-order rate constants against the concentration of catalyst. In the case of catalysis by the conjugate acid of *N*-methylhydroxylamine, a small correction was applied to the observed rate constants to compensate for a slow reaction of this compound with the substrate in the absence of semicarbazide. Since previous work has shown that the attack of semicarbazide on the carbonyl carbon atom is subject to catalysis by the conjugate acid of semicarbazide,³ the catalytic constants for the proton-catalyzed reaction were obtained as follows: at each of several pH values, pseudo-first-order rate constants were measured at three semicarbazide concentrations and the second-order rate constants, $k_2 = k_1/[\text{semicarbazide}]_{\text{free base}}$, were calculated. These were plotted against the concentration of protonated semicarbazide in solution and extrapolated to zero concentration. The values at the intercepts were then plotted against the concentration of hydrogen ion, and the rate constant for the proton-catalyzed reaction was obtained from the slope of this line. This line, when extrapolated to zero hydrogen ion concentration, gave the rate constant for the solvent-catalyzed reaction. The catalytic constant for the water reaction was obtained by dividing the value at the intercept by the molar concentration of water, 55.5. Second-order rate constants for semicarbazone formation in the region of rate-determining carbinolamine dehydration were calculated from the expression, $k_2 = k_1/[\text{semicarbazide}]_{\text{free base}}(f)$ where f is the fraction of total substrate present as the free aldehyde. Division by f , determined from the equilibrium constants for carbinolamine formation, corrects for conversion of the free aldehyde to the carbinolamine addition compound at high semicarbazide concentrations. In cases

(8) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

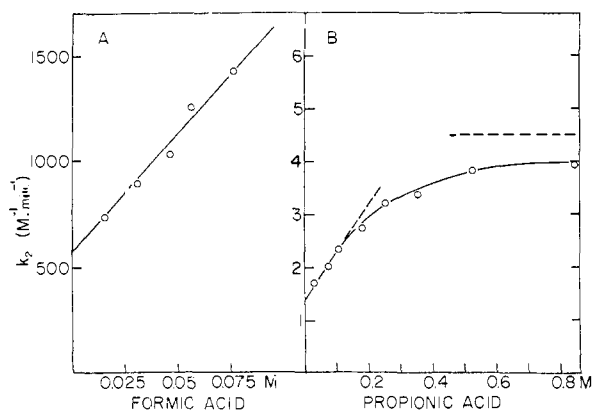


Fig. 2.—(a) Second-order rate constants for *p*-nitrobenzaldehyde semicarbazone formation as a function of formic acid concentration at 25° and pH 3.27. (b) Second-order rate constants for acetophenone semicarbazone formation as a function of propionic acid concentration at 25° and pH 4.10. The horizontal dashed line is the second-order rate constant calculated for rate-determining carbinolamine dehydration.

where this correction is appreciable, equilibrium constants for carbinolamine formation were determined in water.^{3,4} These do not differ by more than 20% from those previously found in 25% ethanol.⁴ The ionic strength of all solutions was maintained at 0.50 by the addition of KCl, except in experiments with acetophenone in which the ionic strength was maintained at 1.0. Measurements of pH were made with a glass electrode and the Radiometer PHM 4b pH meter. Values of *p*D were obtained from the measured pH values and the relation $pD = pH + 0.40$.⁵ This relationship was verified in our system with carefully prepared acetate buffers.

***pK_a* Determinations.**—The *pK_a* of semicarbazide hydrochloride was measured in water at an ionic strength of 0.50 by carefully neutralizing five samples of semicarbazide hydrochloride with known amounts of standard sodium hydroxide. The pH values of these solutions were measured and a *pK_a* of 3.65 ± 0.02 (reported^{2a} 3.66) was obtained from the Henderson-Hasselbach equation. The *pK_a* of semicarbazide hydrochloride in 97% deuterium oxide at ionic strength 0.50 was measured in triplicate by the method of Martin and Butler⁹ with 2,4-dinitrophenol as standard. A K_{H_2O}/K_{D_2O} of 3.28 was obtained, from which a *pK_a* of 4.15 was calculated.

Results

The second-order rate constants, $k_2 = k_1/[\text{semicarbazide}]_{\text{free base}}$, for semicarbazone formation from a series of substituted benzaldehydes and acetophenone are plotted against pH in Fig. 1. At neutral pH, acid-catalyzed dehydration of the carbinolamine intermediate is the rate-determining step and the second-order rate constants are linear in respect to hydrogen ion activity. Under more acidic conditions, the attack of semicarbazide becomes the rate-determining step. As is seen from Fig. 1, the attack of semicarbazide shows both a solvent-catalyzed reaction, predominant between pH 4 and 5, and an acid-catalyzed reaction, predominant below pH 3.¹⁰

(9) D. C. Martin and J. A. V. Butler, *J. Chem. Soc.*, 1366 (1939).

(10) Second-order rate constants for the acid-catalyzed reaction, calculated assuming that this reaction is, in fact, the uncatalyzed attack of the conjugate acid of semicarbazide on the aldehydes, are, in some cases, larger than the second-order rate constants for the attack of the free base of semicarbazide. This result is unreasonable on chemical grounds and indicates that the conjugate acid of semicarbazide is not involved as a nucleophilic reagent in this system.

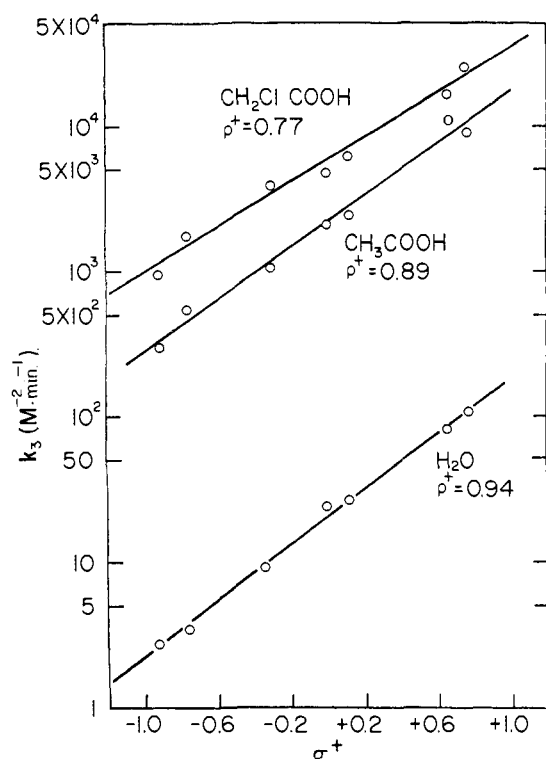


Fig. 3.—Logarithm of catalytic constants for chloroacetic acid, acetic acid and water for the attack of semicarbazide on a series of substituted benzaldehydes at 25° plotted against σ^+ -substituent constants. The benzaldehydes employed and the numerical values of the catalytic constants are listed in Table I.

In Fig. 2a, the second-order rate constants for *p*-nitrobenzaldehyde semicarbazone formation are shown as a function of formic acid concentration at *pH* 3.27, in the region of rate-determining semicarbazide attack (Fig. 1). The second-order rate constants increase linearly with formic acid concentration and show a threefold increase as the catalyst concentration is varied from zero to 0.08 *M*. In Fig. 2b, the second-order rate constants for acetophenone semicarbazone formation are shown as a function of propionic acid concentration at *pH* 4.10, also in the region of rate-determining semicarbazide attack (Fig. 1). At low propionic acid concentrations, the rate constants increase linearly with catalyst concentration, while at higher concentrations, the rate constants level off and eventually become nearly independent of catalyst concentration. The second-order rate constants approach the rate constant for rate-determining carbinolamine dehydration calculated from the data in Fig. 1 and indicated by the horizontal dotted line in Fig. 2b.

Third-order catalytic rate constants for several acids acting as catalysts for attack of semicarbazide on a series of substituted benzaldehydes and on acetophenone are given in Table I. In each case the rate constant was determined, in the region of rate-determining semicarbazide attack, from a linear plot similar to that shown in Fig. 2a. The catalytic constants for chloroacetic acid, acetic acid and water are plotted in Fig. 3 against

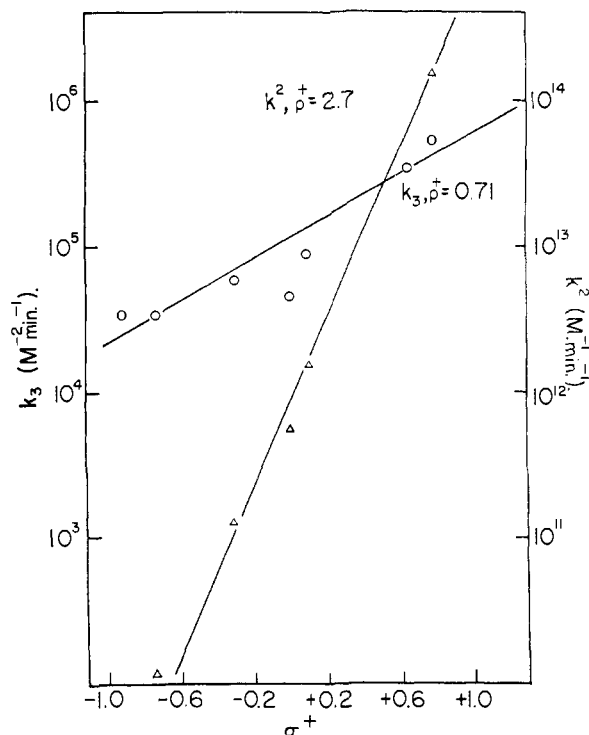


Fig. 4.—Logarithm of catalytic constants for the hydrated proton for the attack of semicarbazide on a series of substituted benzaldehydes (O) and the logarithm of second-order rate constants calculated assuming an attack of semicarbazide on the conjugate acids of the aldehydes (Δ) at 25° plotted against σ^+ -substituent constants.

σ^+ -substituent constants.¹¹ The ρ^+ -values, from the plots in Fig. 3, are: chloroacetic acid, 0.77; acetic acid, 0.89; water, 0.94. In Fig. 4, the catalytic constants for the hydrated proton are plotted against σ^+ -substituent constants, giving a ρ^+ -value of 0.71. In addition, second-order rate constants have been calculated, from the *pK_a* values of the protonated aldehydes¹² and the experimental catalytic constants, for the hypothetical reaction of semicarbazide with the conjugate acids of the benzaldehydes. A plot of these values against σ^+ -substituent constants gives a ρ^+ -value of 2.7 (Fig. 4). In all of the above cases, the data are better correlated by σ^+ -than by σ -substituent constants, except for the case of catalysis by the hydrated proton, for which both sets of substituent constants correlate the data about equally well. The correlation of the catalytic constants with σ^+ , rather than σ , reflects the high degree of stabilization of the starting materials by *para* substituents capable of donating electrons by resonance.¹³

In Table II, first- and second-order rate constants for *p*-chlorobenzaldehyde semicarbazone formation in water and 97% deuterium oxide in 0.08 *M* hydrochloric acid are given. Under these conditions only the acid-catalyzed attack of semicarbazide is kinetically significant (Fig. 1). Since the reactions in deuterium oxide did not proceed to completion,

(11) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

(12) K. Yates and R. Stewart, *Can. J. Chem.*, **37**, 664 (1959).

(13) R. Wolfenden and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 2763 (1961).

TABLE I
CATALYTIC CONSTANTS OF SEVERAL ACIDS FOR THE ATTACK OF SEMICARBAZIDE ON A SERIES OF CARBONYL COMPOUNDS AT 25°^a

Carbonyl compound	Acids								H ₂ O
	H ₃ O ⁺ (× 10 ⁻⁴)	CNCH ₂ - COOH (× 10 ⁻³)	ClCH ₂ - COOH (× 10 ⁻³)	SCH ⁺ ^b (× 10 ⁻³)	HCOOH (× 10 ⁻³)	HOCH ₂ - COOH (× 10 ⁻³)	CH ₃ COOH (× 10 ⁻³)	CH ₃ CH ₂ - COOH (× 10 ⁻³)	
<i>p</i> -Nitrobenzaldehyde	54	31	26		12	9.5	9.3		2.2
<i>m</i> -Nitrobenzaldehyde	34		17				11		1.5
<i>p</i> -Chlorobenzaldehyde	9.0	8.0	6.6	6.5	4.2	4.6	2.5	3.1	0.47
Benzaldehyde	4.3		5.0	7.1			2.2		.43
<i>p</i> -Methylbenzaldehyde	5.5		3.9	2.9			1.1		.17
<i>p</i> -Methoxybenzaldehyde	3.4		1.8	1.3			0.56		.067
<i>p</i> -Hydroxybenzaldehyde	3.4	1.4	1.0	0.76	0.51	0.51	.32		.05
Acetophenone	0.5	0.045	0.041		.023		.010	0.0096	

^a All rate constants have the dimensions $M^{-2} \text{min.}^{-1}$; ionic strength maintained at 0.5 except in the acetophenone experiments, in which the ionic strength was 1.0. ^b The conjugate acid of semicarbazide.

small corrections of the observed rate constants were made using the previously determined equilibrium constant for *p*-chlorobenzaldehyde semicarbazone formation.¹³ In no case did this correction exceed 15%. The observed first-order rate constants are about 3.5 times greater in water than deuterium oxide. The ratio of second-order

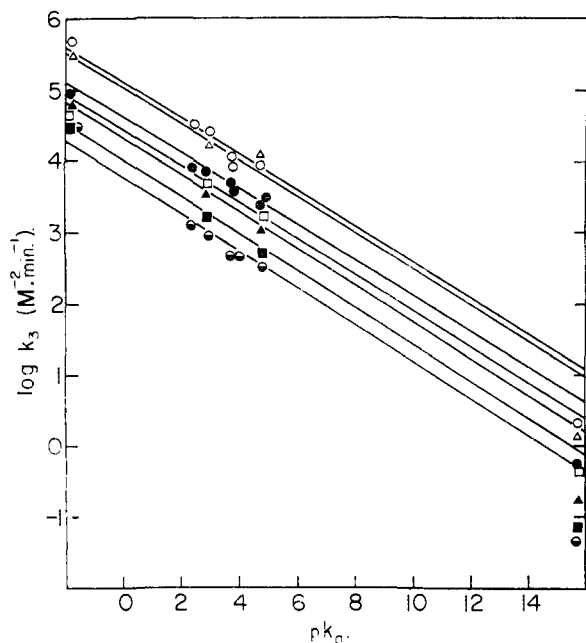


Fig. 5.—Logarithm of the catalytic constants for several acids for the attack of semicarbazide on a series of substituted benzaldehydes at 25° plotted against their respective pK_a values. The acids and the numerical value of the catalytic constants are listed in Table I. The lines are drawn with a slope of 0.25: O, *p*-nitro-; Δ, *m*-nitro-; ●, *p*-chloro-; □, unsubstituted; ▲, *p*-methyl-; ■, *p*-methoxy-; ●, *p*-hydroxybenzaldehyde.

rate constants, k_H/k_D , based on semicarbazide as the free base, is 1.2. In addition, the catalytic constants for acetic acid in water and deuterium oxide, as defined in Table II, were measured and a value of k_H/k_D of 1.6 was obtained (Table II).

In Fig. 5, the catalytic constants listed in Table I are plotted against the respective pK_a values of the catalyzing acids for each of the substituted benzaldehydes. Lines of slope 0.25 have been

TABLE II
DEUTERIUM OXIDE ISOTOPE EFFECT ON CATALYSIS OF THE ATTACK OF SEMICARBAZIDE ON *p*-CHLOROBENZALDEHYDE BY THE HYDRATED PROTON AND ACETIC ACID AT 25° AND IONIC STRENGTH 0.50^b

Solvent	(Semi-carbazide) ^b ($M \times 10^3$)	k_1 (min.^{-1})	k_2 ($\text{min.}^{-1} M^{-1}$)	k_3 ^c ($\text{min.}^{-1} M^{-2}$)	k_H/k_D
Hydrated proton ^d					
H ₂ O	2.82	0.189	6.70		
D ₂ O	0.90	.053	5.90		1.13
H ₂ O	5.64	.365	6.50		
D ₂ O	1.79	.099	5.55		1.17
H ₂ O	11.28	.729	6.45		
D ₂ O	3.58	.191	5.35		1.20
Acetic acid ^e					
H ₂ O	324			2.40	
D ₂ O	324			1.45	1.65

^a The final deuterium oxide content was greater than 97% in all cases. ^b As the free base. ^c $k_3 = k_1/[\text{CH}_3\text{COOH}][\text{semicarbazide}]$ free base. ^d Total acid concentration 0.08 M. ^e Acetic acid concentration varied from 0.04 to 0.16 M, pH 3.91, pD 4.02.

drawn through the points for the carboxylic acids and the hydrated proton. Values of α based on the catalytic constants of the carboxylic acids alone in the reactions with *p*-nitro-, *p*-chloro- and *p*-hydroxybenzaldehydes and acetophenone, compounds for which data for several acids was obtained, do not differ from this value by more than ± 0.05 . The catalytic constants for water fall below the line in the Brønsted plots by a factor of five to ten.

Catalytic constants for thirty acids of varying structure and charge type, acting as catalysts for the attack of semicarbazide on *p*-chlorobenzaldehyde, are collected in Table III, together with the values obtained after correction for statistical factors. Statistical corrections were made by the method of Benson¹⁴; internal corrections for alkyl groups, which do not affect the results, were not made. Statistical corrections were not applied to the data for water and the hydrated proton because of uncertainties in respect to the special structure of these catalysts in aqueous solution. Catalysis by nitroethane, 2-nitropropane and boric acid could not be detected and the indicated cata-

(14) S. W. Benson, *J. Am. Chem. Soc.*, **80**, 5151 (1958).

TABLE III
CATALYTIC CONSTANTS OF ACIDS FOR THE ATTACK OF SEMICARBAZIDE ON *p*-CHLOROBENZALDEHYDE AT 25°^a

Catalyst	pH	Concn. range, M	HA	B	pK_a	pK_a^{corr}	k_{cat} , $M^{-2} \text{ min.}^{-1}$	k_{cat}^{corr} , $M^{-2} \text{ min.}^{-1}$
1. Cyanoacetic acid	2.30	0.02-0.30	1	2	2.45	2.15	8.0×10^3	8.0×10^3
2. Chloroacetic acid	2.50	.03- .30	1	2	2.90	2.60	6.6×10^3	6.6×10^3
3. Formic acid	3.50	.01- .13	1	2	3.75	3.45	4.2×10^3	4.2×10^3
4. Glycolic acid	3.60	.01- .13	1	2	3.81	3.51	4.6×10^3	4.6×10^3
5. Acetic acid	3.92	.04- .16	1	2	4.76	4.46	2.5×10^3	2.5×10^3
6. Propionic acid	3.70	.02- .19	1	2	4.87	4.57	3.1×10^3	3.1×10^3
7. Succinic acid	2.48	.05- .25	2	2	4.19	4.19	9.9×10^3	5.0×10^3
8. Glycine hydroxamic acid	3.33	.01- .08	1	1	7.40	7.40	4.0×10^3	4.0×10^3
9. Formohydroxamic acid	3.37	.05- .25	1	1	8.65	8.65	1.8×10^3	1.8×10^3
10. Acetohydroxamic acid	2.60	.05- .25	1	1	9.40	9.40	1.9×10^3	1.9×10^3
11. Trimethylamine N-oxide hydrochloride	3.40	.02- .10	3	3	4.60	4.60	2.2×10^3	2.2×10^3
12. Arsenate monoanion	3.73	.01- .08	2	3	6.98	6.81	5.4×10^3	2.7×10^3
13. Phosphate monoanion	3.71	.02- .10	2	3	7.21	7.04	5.9×10^3	3.0×10^3
14. N-Methylaniline·HCl	3.65	.004-0.04	2	1	4.85	5.13	4.9×10^3	2.5×10^3
15. N,N-Dimethylaniline·HCl	2.50	.02-0.16	1	1	5.07	5.07	2.6×10^3	2.6×10^3
16. Pyridine·HCl	2.37	.02- .10	1	1	5.17	5.17	6.8×10^3	6.8×10^3
17. Imidazole·HCl	3.65	.01- .08	2	1	6.95	7.25	4.0×10^3	2.0×10^3
18. Glycine ethyl ester·HCl	3.37	.025-0.15	3	2	7.75	7.93	1.7×10^3	1.1×10^3
19. Semicarbazide hydrochloride	2.40- 3.10	.0025-0.01	3	2	3.65	3.83	6.5×10^3	4.3×10^3
20. Morpholine·HCl	3.66	.05-0.25	2	1	8.36	8.66	4.0×10^2	2.0×10^2
21. DABCO·2HCl ^b	3.40	.02- .13	2	1	4.18	4.48	3.8×10^3	1.9×10^3
22. NH ₄ Cl	3.44	.20-1.00	12	3	9.21	9.81	1.7×10^2	0.4×10^3
23. N-Methylhydroxylamine·HCl	3.32	.01-0.10	2	1	5.96	6.26	4.3×10^3	2.2×10^3
24. N,N-Dimethylhydroxylamine·HCl	2.55	.025-0.15	1	1	5.20	5.20	6.9×10^3	6.9×10^3
25. Hydrazoic acid	4.40	.006- .026	1	2	4.72	4.42	3.6×10^3	3.6×10^3
26. Nitroethane	2.60	0.33	2	1	8.6	8.9	$<1.7 \times 10^2$	$<0.9 \times 10^{2c}$
27. 2-Nitropropane	2.60	0.13	2	2	7.74	7.74	$<3.8 \times 10^2$	$<3.8 \times 10^{2c}$
28. Boric acid	2.56	0.08-0.50	3	1	9.23	9.71	$<1.1 \times 10^2$	$<0.7 \times 10^{2c}$

^a Ionic strength maintained at 0.5 by the addition of KCl. ^b 1,4-Diazabicyclo[2.2.2]octane. ^c Catalysis was not detected; catalytic constant calculated on the basis that a rate increase of 10% with increasing catalyst concentration would not have been recognized.

lytic constants are maximum values which were calculated by assuming that a 10% increase in rate with increasing catalyst concentration would not have been recognized. In Fig. 6, the logarithms of the corrected catalytic constants are plotted against the corrected pK_a values. A line of slope 0.25 is drawn through the values for the mono-carboxylic acids and the hydrated proton. If statistical corrections are not made, the deviation of the catalytic constants from the Brönsted line is larger for succinic acid and smaller for ammonium ion; the fit of the remaining values to the Brönsted line is not significantly altered by the statistical corrections. The positive deviation from the line in the Brönsted plot in the case of glycine hydroxamic acid is partially due to the presence of two catalytic groups on the molecule.

Discussion

A. Mechanism of the Reaction.—The observed general acid catalysis of the attack of a nucleophilic reagent on the carbonyl carbon atom may proceed by any of four kinetically indistinguishable mechanisms having transition states which may be represented by I, II, III and IV. Although transition states I and III are formally termolecular, their formation may be visualized as occurring *via* two consecutive bimolecular reactions rather than by a ternary collision in solution. For instance, I may occur by a pre-equilibrium formation of a

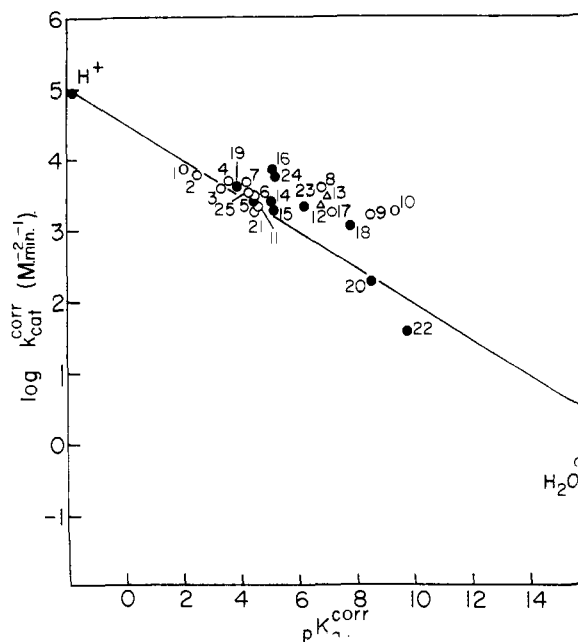
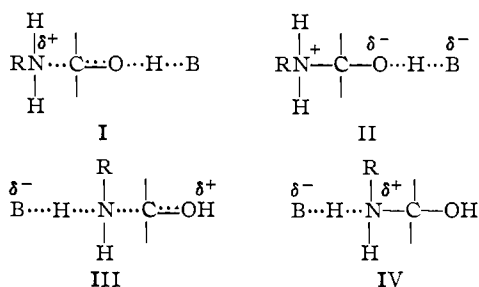


Fig. 6.—Logarithms of catalytic constants for thirty acids for the attack of semicarbazide on *p*-chlorobenzaldehyde at 25° plotted against their respective pK_a values. Acids and numerical values of the rate constants are listed in Table III: O, neutral oxygen acids; ●, nitrogen acids; Δ, anionic oxygen acids.

complex involving a hydrogen bond between a molecule of acid catalyst and the carbonyl oxygen atom, followed by an attack of the nucleophilic reagent on the complex. Transition states I and II involve true general acid catalysis and differ



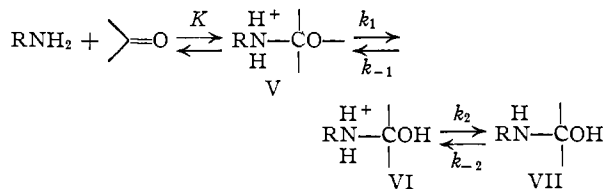
only in the timing of the proton transfer reaction. In I, the proton transfer is concerted with attack of the nucleophilic reagent and aids the latter reaction by increasing the electrophilic character of the carbonyl carbon atom. In II, on the other hand, the proton transfer occurs following a rapid pre-equilibrium formation of addition compound between nucleophilic reagent and carbonyl compound. Transition states III and IV involve specific acid-general base catalysis. Specific acid-general base catalysis, although kinetically indistinguishable, is mechanistically quite different from true general acid catalysis (I or II). In III, the attack of the nucleophilic reagent on the carbonyl carbon atom is aided both by pre-equilibrium protonation of the carbonyl oxygen atom and by conversion of the nucleophilic reagent into a potential amide ion (or alkoxide or thioalkoxide ion in the case of oxygen or sulfur nucleophilic reagents) by partial removal of a proton in the transition state. In IV, the proton removal occurs following a pre-equilibrium formation of the protonated addition product of nucleophilic reagent and carbonyl compound. It is concluded from the arguments developed below that the transition state for general acid catalysis of the attack of semicarbazide on benzaldehydes involves true general acid catalysis with the proton transfer concerted with attack of the nucleophilic reagent (I). More precisely, the transition state involves formation of the N-C bond, accompanied by some movement of hydrogen toward oxygen; the precise timing of the proton transfer is unknown and complete transfer of the proton may occur in a very fast step after the N-C bond is formed, followed by a diffusion-controlled separation of the products.

The strongest evidence against the involvement of protonated aldehydes as intermediates in semicarbazone formation comes from a consideration of the proton-catalyzed reaction. Second-order rate constants were calculated from the known basicities of the aldehydes¹² and the observed third-order rate constants, for a hypothetical mechanism involving attack of semicarbazide on the protonated benzaldehydes. These calculated rate constants are plotted against σ^+ -substituent constants in Fig. 4. The calculated second-order rate constant for the attack of semicarbazide on the conjugate acid of *p*-nitrobenzaldehyde is $1.6 \times 10^{14} M^{-1}$

min.⁻¹ ($2.7 \times 10^{12} M^{-1} \text{sec.}^{-1}$). This value is more than an order of magnitude greater than that for diffusion-controlled reactions in aqueous solution.¹⁵ For example, the measured second-order rate constant for the reaction of the hydrated proton with hydroxide ion,¹⁶ which is the most rapid known reaction of this type, is $1.4 \times 10^{11} M^{-1} \text{sec.}^{-1}$. In addition, no leveling off in rate from that expected on the basis of the $\sigma^+ \rho^+$ plot is seen for the most reactive substrates, indicating that a diffusion-controlled rate is not being approached. Protonated benzaldehydes, therefore, are not involved as intermediates in the proton-catalyzed attack of semicarbazide.

The above line of reasoning may be extended to eliminate protonated aldehydes as intermediates in the general acid-catalyzed reactions as well. This conclusion follows directly since the general base-catalyzed attack of semicarbazide on the protonated aldehydes (III) must be more rapid than the uncatalyzed attack, a reaction which, as we have seen, has a calculated rate constant greater than that for a diffusion-controlled reaction.

The following considerations strongly suggest that the alternative specific acid-general base mechanism, involving transition state IV, is not involved in benzaldehyde semicarbazone formation. In the reaction scheme shown below, if k_2 were the rate-determining step, then VI must be formed in a rapid pre-equilibrium step; that is, k_{-1} must



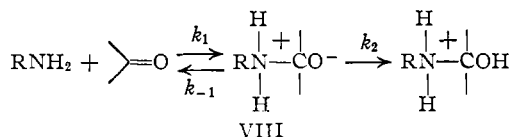
be greater than k_2 . Since proton transfers from the hydrated proton to oxygen and nitrogen bases of greater basicity than water appear to be diffusion controlled,¹⁷ the rates of the reverse reactions must depend only upon the pK_a of the group from which the proton is removed. Therefore, the removal of a proton from the cationic nitrogen atom (pK_a below 4), k_2 , must be more rapid than removal of a proton from the oxygen atom (pK_a near 10),¹⁸ k_{-1} . Consequently, k_2 cannot be the rate-determining step in this reaction sequence and transition state IV is not involved in this reaction. Furthermore, it appears that proton transfer must be concerted with attack of the nucleophilic reagent (I). The alternative reaction mechanism II involves rate-determining proton transfer following pre-equilibrium formation of an addition compound (VIII) between the substrate and nucleophilic reagent. Since the rate of proton transfer from the hydrated proton and other moderately strong acids to VIII is almost certainly diffusion controlled, it is difficult to account for the

(15) M. Eigen and L. De Maeyer, "The Structure of Electrolytic Solutions," W. J. Hamer, ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 64.

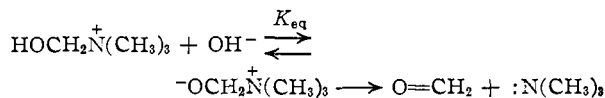
(16) M. Eigen and L. De Maeyer, *Z. Elektrochem.*, **59**, 986 (1955).

(17) (a) A. Weller, *ibid.*, **64**, 55 (1960); (b) M. Eigen, *Suomen Kemi.*, **34A**, 25 (1961); (c) J. Koskikallio, *ibid.*, **34A**, 7 (1961).

(18) Estimated from the pK_a 's of trimethylamine N-oxide (4.6) and choline (13.9).



observed dependence of catalyst effectiveness on acid strength ($\alpha = 0.25$) in terms of this mechanism. Furthermore, in order for the formation of the addition compound to occur in a pre-equilibrium step, the back reaction, k_{-1} , must be faster than the protonation step, k_2 . This is not possible if the protonation is diffusion-controlled.¹⁹ A comparison with the known rate of base-catalyzed decomposition of formocholine chloride suggests that the dissociation step, k_{-1} , is comparatively



slow. Assuming a pK_a of 10 for formocholine, the rate constant for decomposition of the zwitterion intermediate is calculated to be $2 \times 10^4 \text{ sec.}^{-1}$ from the known second-order rate constant for the base-catalyzed decomposition of the cation.²² Formocholine chloride is far from an exact model for VIII, because of the differences in affinity for the carbonyl carbon atom, electron-withdrawing ability and steric effects of the two amines, but the comparison suggests that it is unlikely that the back reaction approaches the rate of the protonation step. Similar considerations cast doubt on a recently proposed mechanism for the general acid-catalyzed hydration of acetaldehyde ($\alpha = 0.54$ ²³), in which it is postulated that a slow proton transfer occurs after a pre-equilibrium addition of water.^{26k}

The above conclusions are consistent with rate data obtained in deuterium oxide solution (Table II). The ratio of second-order rate constants, based on semicarbazide as the free base, k_H/k_D , is 1.2. Since reactions which occur *via* a pre-equilibrium proton transfer, which do not involve proton transfer in the transition state, occur more rapidly in D_2O than in H_2O ,²⁴ due to increased substrate basicity in D_2O ,²⁵ the k_H/k_D ratio greater than unity in the present case indicates that the proton-catalyzed reaction involves general, rather than specific, acid catalysis.

For acetic acid catalysis of *p*-chlorobenzaldehyde semicarbazone formation, $k_H/k_D = 1.6$. Both this value and that obtained for catalysis by the

hydrated proton are small deuterium isotope effects for reactions involving proton transfer in the transition state. Several other examples of this type of behavior have been observed and a number of theoretical justifications have been proposed to account for it.²⁶ The conclusion that a maximum isotope effect occurs only when the proton occupies, in the transition state, a position symmetrical between the two atoms involved in the transfer suggests that in the present transition state the proton is asymmetrically placed between the oxygen atom of the catalyst and the carbonyl oxygen atom. This explanation is consistent with the small Brønsted α -value for benzaldehyde semicarbazone formation (0.25) which indicates, in addition, that little proton transfer has occurred in the transition state.²⁷ One would expect an energy maximum to occur early in a proton transfer reaction only if the proton were transferred to a more basic atom than the one from which it was derived. This requirement is not met by the carbonyl oxygen atom, but is met by the alkoxide ion into which the carbonyl oxygen atom is converted by attack of the nucleophilic reagent. The deuterium isotope effect, together with the small α -value, then suggest that a considerable degree of bond formation between nucleophilic reagent and substrate has occurred in the transition state.

Two additional lines of evidence are consistent with the conclusions reached thus far and suggest, in addition, that the solvent-catalyzed reaction also proceeds *via* a true general acid-catalyzed pathway. First, in the case of each of the substituted benzaldehydes, the catalytic constants for water fall only slightly below the line in the Brønsted plot established by the hydrated proton and carboxylic acids (Fig. 5). Other examples of similar behavior in related reactions have been collected by Bell.²⁸ Secondly, the similarity of the ρ^+ -values for the hydrated proton (0.71), chloroacetic acid (0.77), acetic acid (0.89) and water (0.94) catalyzed reactions (Figs. 3 and 4) suggest a common catalytic pathway for all of these reactions.

In a few related reactions subject to general acid or general base catalysis, evidence has been obtained permitting a distinction between kinetically indistinguishable reaction mechanisms. There are three such examples among reactions involving substrates at the oxidation level of the acyl group. The general base catalysis of the reaction of acetylimidazole with thiols and amines appears to involve partial removal of a proton from the

(19) Since there is good evidence that, in aqueous solution, the carbonyl oxygen atom is hydrogen bonded to at least one molecule of solvent or other acidic species²⁰ and since the fluctuation of a proton across a hydrogen bonded system occurs with frequencies approaching those of infrared stretching vibrations (10^{11} – $10^{14} \text{ sec.}^{-1}$),²¹ it seems likely that the actual rate-determining step in the protonation of VIII would be the diffusion of the product molecule from the conjugate base of the catalyst.

(20) W. P. Jencks, C. Moore, F. Perini and J. Roberts, *Arch. Biochem. Biophys.*, **88**, 193 (1960), and references therein.

(21) M. Eigen and L. De Maeyer, *Proc. Roy. Soc. (London)*, **A247**, 505 (1958).

(22) T. D. Stewart and H. P. Kung, *J. Am. Chem. Soc.*, **55**, 4813 (1933).

(23) R. P. Bell, M. H. Rand and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).

(24) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(25) E. Högfeltd and J. Bigeleisen, *J. Am. Chem. Soc.*, **82**, 15 (1960).

(26) (a) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 3214 (1961);

(b) C. G. Swain and E. R. Thornton, *Tetrahedron Letters*, 211 (1961);

(c) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960; (d) F. H. Westheimer, *Chem. Revs.*, **61**, 265 (1961); (e) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960); (f) D. J. Cram, C. A. Kingsbury and B. Rickborn, *ibid.*,

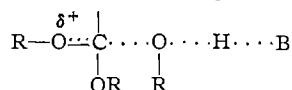
83, 3688 (1961); (g) J. Hine, R. Wiesboeck and R. G. Ghirardelli, *ibid.*, **83**, 1219 (1961); (h) S. D. Ross, M. Finkelstein and R. C. Petersen, *ibid.*, **81**, 5336 (1959); (i) A. V. Willii, *Z. Naturforsch.*, **16A**, 838 (1961); (j) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958);

(k) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960); (l) T. Riley and F. A. Long, *J. Am. Chem. Soc.*, **84**, 522 (1962); (m) F. A. Long and J. Bigeleisen, *Trans. Faraday Soc.*, **55**, 2077 (1959), and references therein.

(27) J. E. Gordon, *J. Org. Chem.*, **26**, 738 (1961).

(28) R. P. Bell, "Acid-Base Catalysis," Oxford University Press London, 1941.

attacking reagent by the catalyst in the transition state since, when the attacking nucleophilic reagent is an oxygen anion with no proton to remove, no general base catalysis is found.²⁹ The general base-catalyzed aminolysis of phenyl acetate appears to proceed by a similar mechanism.^{26e} General acid catalysis of the hydrolysis of orthoesters, if the reaction does not involve solvent as nucleophilic reagent (A-1), must occur by aiding the departure of the leaving alcohol. In the reverse reaction, this corresponds to general base catalysis of the attack of alcohol on a structure analogous to a protonated carbonyl group. Studies of the volume of activation for the acid-catalyzed hydrolysis of formals, acetals and orthoformates indicate that these reactions proceed by an A-1



mechanism.³⁰ However, Kwart and Price have tentatively suggested that the acid-catalyzed hydrolysis of a series of methyl orthobenzoates proceeds by an A-2 mechanism.³¹ In each of the above reactions, the catalysis appears to be directed toward the entering or leaving group (transition states similar to III or IV), while in the case of semicarbazone formation the catalysis is directed toward the substrate.

B. Influence of the Reactivity of the Substrate and Nucleophilic Reagent on General Acid Catalysis.—In this section, relationships between the magnitude of the Brönsted α -value, the reactivity of the substrate and the reactivity of the nucleophilic reagent will be considered. Consider a system of i substrates (characterized by σ_i) and j general acid catalysts (characterized by pK_{a_j}). The Hammett and Brönsted equations for this system are

$$\log k_{i,j} = \log k_{o,j} + \sigma_i \rho_j \quad (4)$$

$$\log k_{i,j} = \log G_i^A - \alpha_i pK_{a_j} \quad (5)$$

Combining 4 and 5 we obtain

$$\log k_{o,j} + \sigma_i \rho_j = \log G_i^A - \alpha_i pK_{a_j} \quad (6)$$

Rewriting 6 for two arbitrary j 's and subtracting yields

$$\log \frac{k_{o,1}}{k_{o,2}} + \sigma_i (\rho_1 - \rho_2) = \alpha_i (pK_{a,2} - pK_{a,1}) \quad (7)$$

The first term on the left hand side of 7 is easily evaluated from 4 and 5

$$\log \frac{k_{o,1}}{k_{o,2}} = \alpha_o (pK_{a,2} - pK_{a,1}) \quad (8)$$

Putting 8 into 7 and rearranging, we obtain

$$\frac{pK_{a,2} - pK_{a,1}}{\rho_2 - \rho_1} = \frac{\sigma_i}{\alpha_o - \alpha_i} \quad (9)$$

The left-hand side of 9 depends only on the nature of the general acid catalysts, while the right-hand side of 9 depends only on the nature of the substrates. Hence the two sides of 9 are independently variable and we have finally

(29) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1280 (1959).

(30) J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, **55**, 809 (1959).

(31) H. Kwart and M. B. Price, *J. Am. Chem. Soc.*, **82**, 5123 (1960).

$$\frac{\sigma_i}{\alpha_o - \alpha_i} = \frac{pK_{a,2} - pK_{a,1}}{\rho_2 - \rho_1} = C_1 \quad (10)$$

A mathematically similar treatment of the Hammett equation has been carried out by Hine and by Ritchie, *et al.*,³² with somewhat different considerations in mind. The general case of multiple variations in structure-reactivity correlations has been treated by Miller, who has pointed out that different parameters affecting a single property are interlocked and may be mutually interdependent.³³ Miller's g , a measure of this interdependence, is analogous to the C constants of eq. 10, 12 and 13.

Equation 10 and the equations developed below are quantitative statements of the considerations of Hammond³⁴ and Leffler.³⁵ Equation 10 states that, as substrate reactivity is varied by a change of substituents, the Brönsted α -value for general acid catalysis will vary linearly with σ . Furthermore, as the nature of the acid catalyst is varied, the variation in the ρ -value for the reaction is linearly related to the variation in the pK_a of the catalyzing acid. The ρ^+ -values obtained in the present case, the resultant of the opposing effects of polar substituents on proton transfer to the substrate and on attack of the nucleophilic reagent, increase slightly from 0.71 to 0.94 as the pK_a of the catalyst is increased. This behavior presumably reflects a smaller degree of bond formation between substrate and nucleophilic reagent in the transition state with stronger catalysts, in accord with the Hammond postulate. Although the variations in ρ^+ are too small to permit a precise evaluation of C_1 , the data do indicate that C_1 is large and positive and lies in the range 10–100. Equation 10 and this large value of C_1 require that α should be insensitive to changes in σ^+ ; this is in agreement with the experimental finding that α does not vary, within experimental error, among the compounds examined. Mechanistically, this insensitivity may be regarded as the result of opposing effects of polar substituents on the transition states for proton transfer and nucleophilic attack. For instance, increasing electron withdrawal both decreases the basicity of the carbonyl oxygen atom, causing the transition state for proton transfer to be reached later in the reaction, and increases the electrophilic character of the carbonyl carbon atom, causing the transition state for nucleophilic attack to be reached earlier in the reaction. Since these two processes appear to be concerted, these effects may largely cancel and the position of the proton in the transition state should be insensitive to changes in the polar substituents; that is, α will be nearly constant. In a reaction involving only proton transfer, behavior of the sort expected on the basis of 10 is observed. Bell and co-workers have observed that, in the general base-catalyzed ionization of ketones, β decreases from 0.89 to 0.42 as the reactivity of the ketone

(32) (a) J. Hine, *ibid.*, **81**, 1126 (1959); (b) C. D. Ritchie, J. D. Saltiel and E. S. Lewis, *ibid.*, **83**, 4601 (1961).

(33) S. I. Miller, *J. Am. Chem. Soc.*, **81**, 101 (1959). See also L. Wilputte-Steinert, P. J. C. Fierens and H. Hannaert, *Bull. Soc. Chim. Belg.*, **64**, 628 (1955).

(34) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(35) J. E. Leffler, *Science*, **117**, 340 (1953).

is increased by ten orders of magnitude.³⁶ A plot of $\beta_0 - \beta_1$ against $\log R_1 - \log R_0$, where R is a measure of substrate reactivity and the appropriate values for *sym*-dichloroacetone were chosen as standards, shows a reasonably good fit to a straight line with a slope near 20.

Employing the Brønsted relationship (5) and the Swain-Scott equation for correlation of the rates of nucleophilic reactions (11)³⁷ for a system of j general acids and n nucleophilic reagents (characterized by n_k), one may derive in a manner

$$\log k_{j,k} = \log k_{j,0} + s_j n_k \quad (11)$$

analogous to that employed above, the relationship:

$$\frac{pK_{a2} - pK_{a1}}{s_1 - s_2} = \frac{n_k}{\alpha_k - \alpha_0} = C_2 \quad (12)$$

Equation 12 states that, as the nature of the nucleophilic reagent is varied, the variation in α is linearly related to the variation in reactivity of the nucleophilic reagent. In addition, as the nature of the general acid catalyst is changed, the variation in susceptibility of the reaction to nucleophilic attack varies linearly with the variation in pK_a of the catalyzing acid. Reasoning from the Hammond postulate, the transition state should be reached earlier in the course of the reaction as the reactivity of the nucleophilic reagent is increased and α , therefore, will decrease with increasing nucleophilicity; that is, C_2 should be negative. Data relevant to this point (Table IV) indicate that α does, in fact, decrease with increasing reactivity of the nucleophilic reagent, indicating that the catalyst becomes less selective toward the nucleophilic reagent as the reactivity of the nucleophilic reagent increases. Equations 12 and 13 (see below) may be generalized to include electrophilic reactions by the substitution of e , a measure of electrophilicity, for n . In those nucleophilic reactions in which the basicity of the nucleophilic reagent is a good measure of nucleophilicity, the pK_a of the conjugate acid of the nucleophilic reagent may be used in place of n .

TABLE IV

BRONSTED α -VALUES FOR THE ATTACK OF SEVERAL NUCLEOPHILIC REAGENTS ON THE CARBONYL CARBON ATOM

Substrate	Nucleophilic reagent	pK_a	α
Acetaldehyde	Water	-1.74	0.54 ^a
<i>sym</i> -Dichloroacetone	Water	-1.74	.27 ^a
Benzaldehydes	Semicarbazide	3.65	.25 ^b
<i>p</i> -Chlorobenzaldehyde	Aniline	4.60	.25 ^c
Benzaldehyde	Hydroxylamine	5.97	Near zero ^d
Aliphatic aldehydes	Cyanide	9.40	Near zero ^e
Formaldehyde	Trimethylamine	9.76	Near zero ^f

^a Ref. 41. ^b This study. ^c E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 832 (1962). ^d Ref. 3. ^e W. J. Svirbely and J. F. Roth, *J. Am. Chem. Soc.*, **75**, 3106 (1953). ^f Ref. 31; this reaction is the reverse of the decomposition of formocholine chloride (see text). Since the decomposition reaction shows only specific base catalysis (β near 1), the formation reaction must be predominantly uncatalyzed (α near zero).

(36) (a) R. P. Bell and J. Hansson, *Proc. Roy. Soc. (London)*, **A265**, 214 (1960); (b) R. P. Bell and O. M. Lidwell, *ibid.*, **A176**, 88 (1940); (c) R. P. Bell, E. Gelles and E. Möller, *ibid.*, **A198**, 308 (1949); (d) R. P. Bell, *Trans. Faraday Soc.*, **39**, 253 (1943).

(37) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

A final relationship may be developed analogous to 10 and 12 for a system of i substrates and k nucleophilic reagents. Employing 4 and 11 and proceeding as before, one obtains

$$\frac{\sigma_i}{s_i - s_0} = \frac{n_1 - n_2}{\rho_1 - \rho_2} = C_3 \quad (13)$$

(for electrophilic reactions, the second term is $(e_1 - e_2)/(\rho_1 - \rho_2)$). Equation 13 states that, as the reactivity of the substrate is altered, the variation in susceptibility to nucleophilic attack varies linearly with σ . Furthermore, as the nature of the nucleophilic reagent is varied, the variation in ρ for the reaction is a linear function of the variation in reactivity of the nucleophilic reagent. C_3 is small for electrophilic substitution reactions, which become less selective as the reactivity of the electrophilic reagent is increased.³⁸ In aromatic alkylations, ρ varies one unit for a variation of five orders of magnitude in the reactivity of the electrophilic reagent and in aromatic halogenations, ρ varies 1.5 units for a change of three orders of magnitude in the reactivity of the electrophilic reagent.³⁹ Employing $\log k_0$ values as a measure of e , C_3 is near 5 for the alkylation reactions and near 2 for the halogenation reactions. On the other hand, Knowles, *et al.*,⁴⁰ have observed that ρ -values for the attack of substituted phenoxide ions on chlorinated nitrobenzenes, which in this case reflect susceptibility of the substrate to changes in reactivity of the nucleophilic reagent, do not vary appreciably as the reactivity of the substrate is varied by four orders of magnitude, indicating that C_3 is large for this reaction.

C. The Relationship of Catalytic Efficiency to Catalyst Structure and Charge Type.—Thirty acids of widely varying structure and charge type have been studied as catalysts for the attack of semicarbazide on *p*-chlorobenzaldehyde (Table III). In Fig. 6, the catalytic constants have been plotted against the appropriate pK_a values and a line ($\alpha = 0.25$) drawn through the points for the carboxylic acids and the hydrated proton. Although most of the points fall near the line, ten acids have catalytic constants three-to fivefold greater than predicted from the Brønsted plot. These deviations are small but, since the reaction is relatively insensitive to changes in the strength of the acid catalyst, the deviations may be expected to be small. The abnormally effective catalysts include the monoanions of phosphate and arsenate, the hydroxamic acids and several, but not all, of the substituted ammonium ions. An additional class of compounds, ring-substituted anilinium ions, are several orders of magnitude more effective as catalysts than predicted from the Brønsted plot.⁴¹ However, these compounds function *via* nucleophilic, rather than general acid, catalysis.⁴¹

In the general base-catalyzed decomposition of nitramide, catalysts of different charge obey

(38) G. A. Olah, S. J. Kuhn and S. H. Flood, *ibid.*, **83**, 4571 (1961), and references therein.

(39) Y. Ogata and I. Tabushi, *Bull. Chem. Soc. Japan*, **34**, 604 (1961), and references therein.

(40) J. R. Knowles, R. O. C. Norman and J. H. Prosser, *Proc. Chem. Soc.*, 341 (1961).

(41) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 826 (1962).

different Brønsted relationships.⁴² However, this type of behavior does not account for the deviations observed in the present case. The abnormal catalytic efficiencies of the hydroxamic acids and carbon acids may reflect differences in the amount of structural reorganization that these acids undergo on ionization compared to carboxylic acids.^{43,44} This hypothesis, however, does not explain why the conjugate acids of morpholine and triethylenediamine (DABCO) are normal catalysts while the conjugate acid of pyridine is an abnormally effective catalyst.

A situation similar to the present one is seen in the general acid-catalyzed mutarotation of glucose, in which a number of small deviations from the Brønsted relationship have been observed as catalyst structure and charge type are varied.⁴⁵ This type of behavior does not appear to have a simple explanation. For instance, pyridinium ion is abnormally effective compared to carboxylic acids as a catalyst for the decarboxylation of aromatic acids⁴⁶ and for benzaldehyde semicarbazone formation, but falls on the same line with carboxylic acids in the general acid-catalyzed hydration of acetaldehyde,²⁸ and pyridine falls on the same line with carboxylate anions in the general base-catalyzed bromination of ethyl nitroacetate.⁴⁷ Furthermore, in the present case, the phosphate monoanion is an abnormally effective catalyst and the ammonium ion is an abnormally ineffective catalyst, while in the exchange of aromatic protons both catalysts possess normal

catalytic properties.⁴⁸ The occurrence of such deviations is not surprising in view of the considerable number of factors upon which catalyst efficiency may depend: (a) the equilibrium constant for the formation of a hydrogen-bonded complex between catalyst and substrate; (b) the amount of polarization of the carbonyl group by the catalyst, which facilitates attack of the nucleophilic reagent; (c) the rate of proton transfer between catalyst and substrate; (d) in some reactions, the rate of diffusion of product from the conjugate base of the catalyst following proton transfer. While these properties may be individually correlated with the acidity of the catalyst, the over-all catalytic efficiency may be expected to be somewhat different for different types of acids.

D. Further Evidence for a Change in the Rate-determining Step in Semicarbazone Formation.—The second-order rate constants for acetophenone semicarbazone formation at pH 4.10 increase linearly with increasing concentrations of propionic acid at first, then level off and eventually become essentially independent of catalyst concentration (Fig. 2b). The second-order rate constants approach that calculated for rate-determining carbamoylamine dehydration and this behavior, therefore, constitutes additional evidence for a change in the rate-determining step of the reaction.^{3,4} Similar behavior has been observed for the general acid-catalyzed decomposition of diazoacetate ion⁴⁹ and has been interpreted in terms of a change in rate-determining step.⁵⁰

Acknowledgment.—We are grateful to Dr. Kenneth Kustin for a helpful discussion regarding rates of proton transfer reactions.

(42) Reference 28, p. 86.

(43) R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc. (London)*, **A197**, 141 (1949); see also R. P. Bell and M. B. Jensen, *ibid.*, **A261**, 38 (1961).

(44) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(45) Reference 28, p. 88.

(46) A. V. Willi, *Trans. Faraday Soc.*, **55**, 433 (1959).

(47) R. P. Bell and T. Spencer, *Proc. Roy. Soc. (London)*, **A251**, 41 (1959).

(48) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961).

(49) C. V. King and E. D. Bolinger, *ibid.*, **58**, 1533 (1936).

(50) R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 2983 (1960).