# Kinetics and Mechanism for Benzaldehyde Phenylhydrazone Formation[1]

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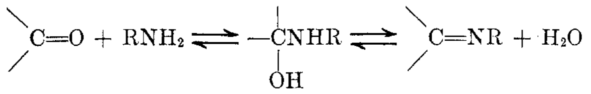
Benzaldehyde phenylhydrazone formation, like semicarbazone, thiosemicarbazone, oxime, and Schiff base formation, occurs with rate-determining attack of the nucleophilic reagent under slightly acidic conditions and with rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions. The attack of phenylhydrazine on *p*-chloro-, unsubstituted, *p*-methoxy-, and *p*-hydroxybenzaldehyde is subject to general acid catalysis by carboxylic acids and the conjugate acid of the nucleophile while that on *p*-nitrobenzaldehyde is subject to catalysis by carboxylic acids and apparent inhibition by carboxylate ions. Rate constants for the hydrated proton, chloroacetic acid, acetic acid, phenylhydrazinium ion, and water as catalysts for the attack of phenylhydrazine on a series of substituted benzaldehydes are well correlated by the $\sigma^+$ substituent constants. The derived values of $\rho^+$ increase linearly with increasing p$K_a$ of the catalyst. The dehydration of the carbinolamines derived from phenylhydrazine and benzaldehydes exhibits both acid-catalyzed and pH-independent reactions and, in the case of that derived from *p*-nitrobenzaldehyde, a base-catalyzed reaction as well.

The addition of amines to carbonyl compounds has been the subject of a number of studies in recent years. Two excellent reviews of this topic have appeared.[3,4]

It has been established that the formation of oximes,[5] semicarbazones,[5,6] thiosemicarbazones,[7] phenylhydrazones,[8] and Schiff bases[9-12] occurs with rate-determining attack of the nucleophilic reagent under slightly acidic conditions. This step is generally subject to both general acid and specific acid catalysis for the cases of weakly basic amines but is insensitive to such catalysis when the nucleophile is strongly basic.[3,4] Under neutral or basic conditions, dehydration of the carbinolamine becomes the rate-determining step. This



$$>C{=}O + RNH_2 \rightleftharpoons -\overset{|}{\underset{OH}{C}}NHR \rightleftharpoons\ >C{=}NR + H_2O \qquad (1)$$

step is generally subject to strong acid catalysis although pH-independent and base-catalyzed processes also occur in some cases (eq 1).[3,4,7]

In this work, a previous study[8] of benzaldehyde phenylhydrazone formation has been elaborated to include a series of substituted benzaldehydes. Attention is focused on the susceptibility of the various steps to acid catalysis and on the influence of substituents on the pertinent rate constants. While the results are generally consistent with those observed previously in a parallel study of semicarbazone formation,[6] several differences were found. Details are presented herein.

## Experimental Section

**Materials.**—All reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized before use. Solutions of phenylhydrazine were prepared just prior to use. Solutions of carboxylic acids in 20% ethanol were prepared just prior to use to avoid esterification.

**Kinetic measurements** were carried out spectrophotometrically at 25° with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. The reaction of benzaldehyde and phenylhydrazine was followed by observing the appearance of the product at 340 nm (*p*-hydroxybenzaldehyde at 330, *p*-methoxybenzaldehyde at 340, *p*-chlorobenzaldehyde at 348, and *p*-nitrobenzaldehyde at 420 nm), with an initial concentration of aldehyde of $5 \times 10^{-5}$ *M*. In all cases, a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from slopes of plots of log ($OD_\infty - OD_t$) against time in the usual manner. Second-order rate constants were obtained by dividing the first-order constants by the concentration of nucleophilic reagent in the reactive, free base form. When necessary, corrections for catalysis by the conjugate acid of the nucleophile were made as previously described.[6] Kinetic measurements were carried out in 20% ethanol at an ionic strength of 0.50, maintained with KCl, in the presence of $2 \times 10^{-4}$ *M* EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d meter.

Sayer and Jencks have pointed out that neglecting the influence of the rate of carbinolamine dehydration on rate constants measured under conditions in which amine addition is predominantly rate determining can introduce appreciable errors into rate constants for the latter process.[7] The necessary correction takes the form: $k_{addn} = k_{uncor}/(1 - k_{uncor}/k_{dehyd}\ a_{H^+})$ in which $k_{addn}$ is the second-order rate constant for the addition reaction, $k_{uncor}$ is the uncorrected (measured) second-order rate constant for this reaction, $k_{dehyd}$ is the third-order rate constant for acid-catalyzed carbinolamine dehydration, and $a_{H^+}$ is the hydrogen ion activity. It has been clearly shown that it is important to make these corrections for both thiosemicarbazone and semicarbazone formation from benzaldehydes.[7] In the present case, such a correction introduces no appreciable changes in the rate constants under consideration. Clearly, the importance of the correction depends principally upon the relative magnitudes of the third-order rate constants for acid-catalyzed carbinolamine dehydration and acid-catalyzed amine attack; the greater the ratio between these constants, the less important becomes the correction. In the case of semicarbazone formation from *p*-nitrobenzaldehyde, the ratio of these rate constants is 20;[6] in contrast, the same ratio for phenylhydrazone formation from this substrate is 150. Consequently, provided that one does not employ a pH too near that at which dehydration becomes rate-determining or too high buffer concentrations, the correction for phenylhydrazone formation from *p*-nitrobenzaldehyde is negligible. The necessary precautions have been observed and actual calculations of second-order rate constants with and without the correction usually differ by less than 3%. For the other aldehydes employed in the present study, the correction is even less important.

## Results

Figure 1 exhibits the curves obtained by plotting second-order rate constants for the reaction of phenyl-

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[2] This investigtion was carried out by M. P. Bastos during the tenure of a Fellowship from the Fundacão de Amparo a Pesquisa do Estado de São Paulo.

[3] W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

[4] W. P. Jencks, *Progr. Phys. Org. Chem.*, **2**, 73 (1964).

[5] W. P. Jencks, *J. Amer. Chem. Soc.*, **81**, 475 (1959).

[6] E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962).

[7] J. M. Sayer and W. P. Jencks, *ibid.*, **91**, 6353 (1969).

[8] L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966).

[9] E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962).

[10] J. Hine, F. A. Via, J. K. Gotkis, and J. C. Craig, Jr., *ibid.*, **92**, 5186 (1970).

[11] J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *ibid.*, **92**, 5194 (1970).

[12] A. Williams and M. L. Bender, *ibid.*, **88**, 2508 (1966).

TABLE I

CATALYTIC CONSTANTS OF SEVERAL ACIDS FOR THE ATTACK OF PHENYLHYDRAZINE ON A SERIES OF BENZALDEHYDES IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50[a]

| Benzaldehyde | $H_3O^+$ × $10^{-5}$ | CNAcOH × $10^{-4}$ | ClAcOH × $10^{-4}$ | $HCO_2H$ × $10^{-4}$ | $BrCH_2AcOH$ × $10^{-3}$ | AcOH × $10^{-3}$ | $PHH^+$[b] × $10^{-4}$ | $H_2O$[c] |
|---|---|---|---|---|---|---|---|---|
| *p*-Nitrobenzaldehyde | 30 | 39 | 32 | 13 | 90 | 55 | 7.3 | 7 |
| *p*-Chlorobenzaldehyde | 12 | 7.6 | 6.6 | 4.0 | 37 | 17 | 23 | 23 |
| Benzaldehyde[d] | 9.0 | 9.5 | 5.9 | 5.0 | 54 | 15 | 22 | 20 |
| *p*-Methoxybenzaldehyde | 1.6 | 1.7 | 1.0 | 0.47 | 6.5 | 2.2 | 2.3 | 2 |
| *p*-Hydroxybenzaldehyde | 1.7 | 1.3 | 0.96 | 0.40 | 3.4 | 1.7 | 1.4 | 1.5 |

[a] Catalytic constants have the units $M^{-2}$ min$^{-1}$. [b] Phenylhydrazinium ion. [c] Reference 8, with exception of the value for AcOH. [d] Approximate values.

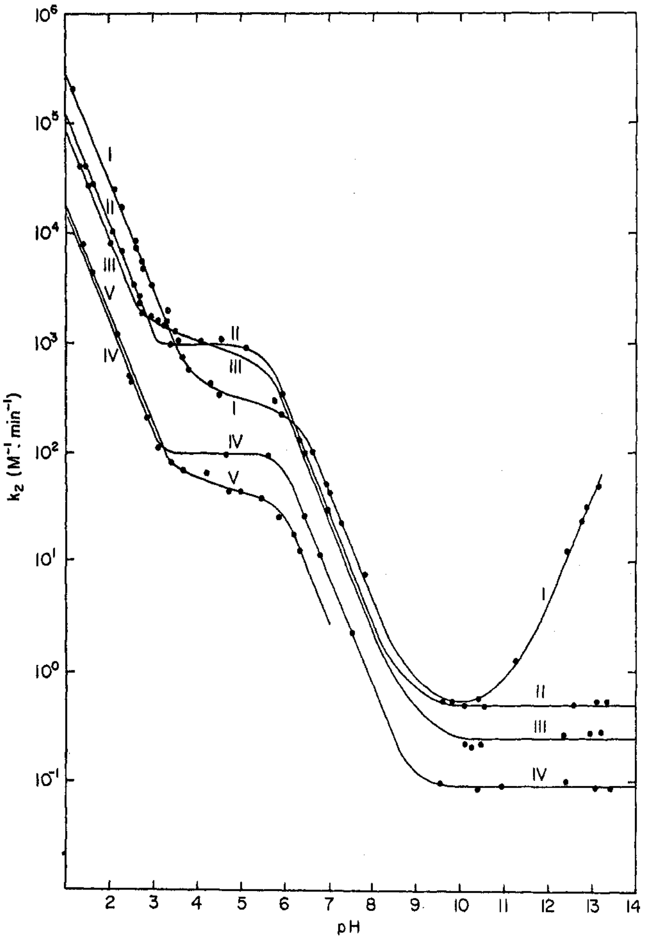

Figure 1.—Logarithms of second-order rate constants for substituted benzaldehyde phenylhydrazone formation in 20% ethanol at 25° and ionic strength 0.50 plotted as function of pH. All points are extrapolated to zero buffer concentration. Curve I, *p*-nitrobenzaldehyde; II, *p*-chlorobenzaldehyde; III, benzaldehyde; IV, *p*-methoxybenzaldehyde; and V, *p*-hydroxybenzaldehyde.

hydrazine with various para-substituted benzaldehydes in 20% ethanol, at 25° and ionic strength 0.50, as a function of pH. Each rate constant shown was obtained by extrapolation to zero buffer concentration. The pH-rate dependence is related to that previously obtained for the formation of benzaldehyde semicarbazones[6] and thiosemicarbazones,[7] of benzaldehyde phenylhydrazone,[8] and of benzaldehyde oxime[8] and may be interpreted in the same manner.[3-9]

Under conditions more acidic than pH 6 (Figure 1), in which attack of phenylhydrazine is rate determining, second-order rate constants for phenylhydrazone formation from each of the benzaldehydes are sensitive functions of the nature and concentration of the carboxylic acid–carboxylate buffer employed to maintain constant pH. Except in one case (see below) buffers employed include cyanoacetate, chloroacetate, formate, β-bromopropionate, and acetate, each at concentrations of 0.05, 0.10, 0.15, 0.20, and 0.25 *M*.

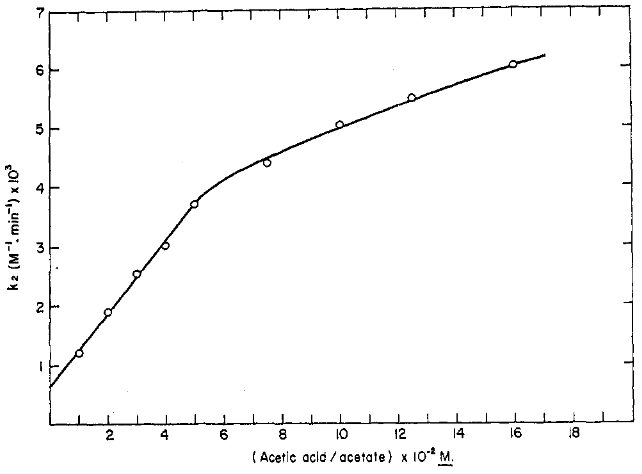

Figure 2.—Second-order rate constants for *p*-nitrobenzaldehyde phenylhydrazone formation as a function of acetic acid plus acetate buffer concentration in 20% ethanol, at 25° and ionic strength 0.50, pH 3.87.

With the exception of *p*-nitrobenzaldehyde, the buffer catalysis for phenylhydrazone formation proved straightforward; measurement of the catalytic effect as a function of the ratio of acidic and basic forms of the buffers established that the catalysis is, within experimental error, of the general acid type. That is, slopes of plots of second-order rate constants against the concentration of the acidic component of the buffer yield straight lines with equal slopes regardless of the buffer composition. Catalytic constants were obtained directly from these slopes. Such behavior is concordant with that previously observed for benzaldehyde phenylhydrazone formation in particular[8] and with reactions of this class generally.[3,4] The catalytic rate constants derived from the data in Figure 1 and from the studies or buffer catalysis are collected in Table I.

*p*-Nitrobenzaldehyde exhibits unique behavior in its reaction with phenylhydrazine. In the first place, plots of second-order rate constants against buffer concentration were generally nonlinear; one example, for catalysis by acetate buffers, is shown in Figure 2. Note that the plot is straight up to a concentration of about 0.10 *M* total buffer and then appears to approach a limiting rate constant with further increases in buffer concentration. Related behavior was observed for other buffer systems. As a consequence of this behavior, quantitative evaluation of buffer effects for the attack of phenylhydrazine on *p*-nitrobenzaldehyde has been restricted to buffer concentrations of not more than 0.10 *M*.

In the second place, the behavior exhibited in Figure 2 may be accounted for in terms of inhibition of the reaction by carboxylate ions, although other explanations are in theory possible (see Discussion).

In Table II, second-order rate constants for this reaction are collected as a function of the concentration of several buffers at various degrees of neutralization. Plots of these rate constants against the concentration of the acidic and basic components of these buffers yield straight lines (deviations are observed at higher buffer concentrations) whose slopes are collected in Table III. Note that neither of the slopes is constant indicating that the catalysis is neither simple general acid nor simple general base. In fact, both sets of slopes decrease with increasing fraction of the basic component of the buffer suggesting a combination of general acid catalysis and carboxylate inhibition.

TABLE II

VARIATION OF SECOND-ORDER RATE CONSTANTS FOR ATTACK OF PHENYLHYDRAZINE ON *p*-NITROBENZALDEHYDE IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50 AS FUNCTION OF THE CONCENTRATION OF SEVERAL CARBOXYLIC ACID–CARBOXYLATE BUFFERS[a]

Cyanoacetate Buffers

| Total buffer concn, *M* | % of buffer in basic form | | |
|---|---|---|---|
| | 20, pH 2.24 | 50, pH 2.75 | 80, pH 3.23 |
| 0.020 | 21 | 7.1 | 2.5 |
| 0.040 | 24 | 9.2 | 3.2 |
| 0.060 | 30 | 11 | 3.9 |
| 0.080 | 34 | 13 | 4.6 |
| 0.10 | 39 | 15 | 5.3 |

Chloroacetate Buffers

| Total buffer concn, *M* | % of buffer in basic form | | |
|---|---|---|---|
| | 20, pH 2.62 | 50, pH 2.95 | 80, pH 3.31 |
| 0.020 | 11 | 5.0 | 2.9 |
| 0.040 | 14 | 6.4 | 3.7 |
| 0.060 | 17 | 8.3 | 4.4 |
| 0.080 | 21 | 10 | 5.1 |
| 0.10 | 24 | 12 | 5.8 |

Formate Buffers

| Total buffer concn, *M* | % of buffer in basic form | | |
|---|---|---|---|
| | 20, pH 3.17 | 50, pH 3.81 | 80, pH 4.30 |
| 0.020 | 4.5 | 0.88 | 0.54 |
| 0.040 | 5.3 | 1.2 | 0.63 |
| 0.060 | 6.1 | 1.4 | 0.67 |
| 0.080 | 6.8 | 1.6 | 0.74 |
| 0.10 | 7.1 | 1.7 | 0.79 |

Bromopropionate Buffers

| Total buffer concn, *M* | % of buffer in basic form | | |
|---|---|---|---|
| | 10, pH 3.31 | 20, pH 3.62 | 30, pH 3.84 |
| 0.010 | 2.2 | 1.3 | 0.95 |
| 0.020 | 3.0 | 1.9 | 1.4 |
| 0.030 | 3.6 | 2.5 | 1.9 |
| 0.040 | 4.3 | 3.0 | 2.3 |
| 0.050 | 5.0 | 3.6 | 2.7 |

Acetate Buffers

| Total buffer concn, *M* | % of buffer in basic form | | |
|---|---|---|---|
| | 10, pH 3.82 | 15, pH 4.03 | 20, pH 4.52 |
| 0.010 | 1.0 | 0.81 | 0.49 |
| 0.020 | 1.4 | 1.1 | 0.64 |
| 0.030 | 1.7 | 1.3 | 0.77 |
| 0.040 | 2.1 | | |
| 0.050 | 2.5 | | |

[a] Rate constants have the units of $M^{-1}$ min$^{-1}$ and have been multiplied by $10^{-3}$.

TABLE III

SLOPES OF PLOTS OF SECOND-ORDER RATE CONSTANTS FOR ATTACK OF PHENYLHYDRAZINE ON *p*-NITROBENZALDEHYDE IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50 AGAINST THE CONCENTRATION OF CARBOXYLIC ACID–CARBOXYLATE BUFFERS[a]

| pH | % of buffer in basic form | Concn range, *M* | Slope ($RCO_2H$) | Slope ($RCO_2^-$) |
|---|---|---|---|---|
| | | Cyanoacetate Buffers | | |
| 2.24 | 20 | 0.02–0.10 | 35 | 54 |
| 2.75 | 50 | 0.02–0.10 | 32 | 16 |
| 3.23 | 80 | 0.02–0.10 | 24 | 4.0 |
| | | Chloroacetate Buffers | | |
| 2.62 | 20 | 0.02–0.10 | 25 | 48 |
| 2.95 | 50 | 0.02–0.10 | 19 | 17 |
| 3.31 | 80 | 0.02–0.10 | 13 | 5.0 |
| | | Formate Buffers | | |
| 3.17 | 20 | 0.02–0.10 | 9.6 | 38 |
| 3.81 | 50 | 0.02–0.10 | 5.6 | 4.9 |
| 4.30 | 80 | 0.02–0.10 | 3.2 | 0.85 |
| | | β-Bromopropionate Buffers | | |
| 3.31 | 10 | 0.01–0.05 | 8.1 | 41 |
| 3.62 | 20 | 0.01–0.05 | 7.4 | 18 |
| 3.84 | 30 | 0.01–0.05 | 7.0 | 9.7 |
| | | Acetate Buffers | | |
| 3.82 | 10 | 0.01–0.05 | 4.1 | 35 |
| 4.03 | 15 | 0.01–0.05 | 3.2 | 16 |
| 4.52 | 20 | 0.01–0.05 | 2.2 | 3.9 |

[a] The slopes have the units of $M^{-2}$ min$^{-1}$ and have been multiplied by $10^{-4}$.

For calculation of the concentration of the acidic component of the buffers, values of $\mathrm{p}K_a$ which refer to water have been used throughout. Since the solvent employed is 20% ethanol in water, which will have the effect of raising the $\mathrm{p}K_a$ value about 0.4 units,[13] it is important to ensure that the unusual results obtained with *p*-nitrobenzaldehyde do not reflect simply the choice of $\mathrm{p}K_a$ values. Note that the use of an ionic strength of 0.50 will diminish the $\mathrm{p}K_a$ values by about 0.2 units, compensating in part for the effect of the partially organic solvent. Three lines of evidence establish that the unusual behavior encountered for catalysis of the attack of phenylhydrazine on *p*-nitrobenzaldehyde is real. In the first place, this behavior is observed only with the indicated substrate; were a systematic error being introduced through use of inappropriate values of $\mathrm{p}K_a$, similar behavior ought to have been observed for all of the aldehydes. In the second place, the trend toward decreasing catalytic constants with increasing fraction of base present is also observed if one employs the concentrations of the acidic species added to the solution rather than those calculated from values of pH and $\mathrm{p}K_a$. Finally, choice of a value of $\mathrm{p}K_a$ lower than the true one has the effect of diminishing the calculated concentration of the acidic component for all values of pH but with greatest effect for the most basic solutions. This would result in increasing catalytic constants with increasing pH, just the opposite of the observed behavior. If anything, use of the indicated values of $\mathrm{p}K_a$

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[13] B. Gutbezahl and E. Grunwald, *J. Amer. Chem. Soc.*, **75**, 565 (1952), and references cited therein.

has tended to diminish the observed trend, not to accentuate it.

Inhibition by the carboxylate ions can be accounted for by assuming the formation of unreactive adducts between the aldehyde and these ions (eq 2). Defining

$$NB + A^- \rightleftharpoons U^- \qquad (2)$$

$K_e$ as the association constant for eq 2, the rate law for the reaction becomes

$$k_2 = \frac{k_0 + k_{HA}(HA) + k_H(H^+)}{1 + K_e(A^-)} \qquad (3)$$

The data of Table III have been fitted to eq 3 by least-squares analysis employing a computer; the best values for catalytic constants for *p*-nitrobenzaldehyde have been included in Table I and the best values of $K_e$ are collected in Table IV.

TABLE IV

APPARENT ASSOCIATION CONSTANTS FOR FORMATION OF UNREACTIVE ADDUCTS BETWEEN CARBOXYLATE IONS AND *p*-NITROBENZALDEHYDE IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50

| Inhibitor | $pK_b$ | $K_e$, $M^{-1}$ |
|---|---|---|
| $CNAcO^-$ | 11.55 | 2.3 |
| $ClAcO^-$ | 11.10 | 4.6 |
| $HCO_2^-$ | 10.25 | 5.1 |
| $BrCH_2AcO^-$ | 10.00 | 5.7 |
| $AcO^-$ | 9.24 | 8.8 |

The attack of phenylhydrazine on benzaldehydes is also susceptible to catalysis by the phenylhydrazinium ion, since second-order rate constants, determined at pH 5.2, increase as a function of the phenylhydrazine concentration. Plots of the second-order rate constants against concentration of phenylhydrazinium ion has permitted determination of the values of the catalytic constants for that acid; these are included in Table I.

Correlation of the catalytic constants of carboxylic acids for substituted benzaldehyde phenylhydrazone formation in Brønsted plots by least-square analysis yields the following values for $\alpha$: *p*-hydroxybenzaldehyde,0.35; *p*-methoxybenzaldehyde,0.36; *p*-chlorobenzaldehyde, 0.36; and *p*-nitrobenzaldehyde, 0.36. The values determined in this work for substituted benzaldehydes are significantly greater than that previously determined for benzaldehyde itself.[8]

The equilibrium constant $K_e$, defined by eq 2 (Table IV), for the formation of unreactive adducts between *p*-nitrobenzaldehyde and carboxylate ions, have been correlated with appropriate values of $pK_b$ in a Brønsted plot. By least-square analysis, a value of 0.25 for $\beta$ has been obtained.

In Figure 3, values of the catalytic constants for the hydrated proton, chloroacetic acid, acetic acid, phenylhydrazinium ion, and water are plotted against the $\sigma^+$ substituent constants.[14] In all cases good correlations have been obtained with the exception of the point for the catalytic constant of water for phenylhydrazine attack on *p*-nitrobenzaldehyde. The $\rho^+$ values are as follows: hydrated proton, 0.86; chloroacetic acid, 0.95; acetic acid, 0.98; phenylhydrazinium ion, 1.0; and water, 1.2. There is better correlation between the catalytic constants and $\sigma^+$ than $\sigma$, which reflects the high degree of stabilization of carbonyl compounds by para substituents capable of donating electrons by resonance. Related results have been obtained for benzaldehyde semicarbazone formation.[6]

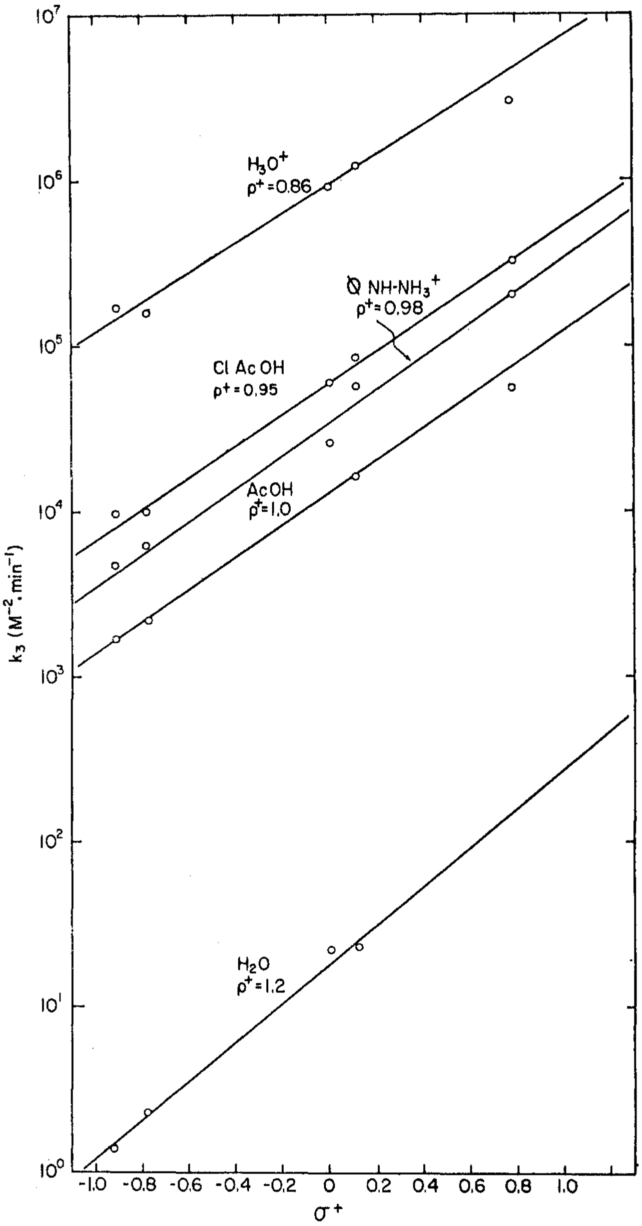

Figure 3.—Logarithms of catalytic constants for the hydrated proton, chloroacetic acid, acetic acid, phenylhydrazinium ion, and water for the attack of phenylhydrazine on a series of substituted benzaldehydes in 20% ethanol, at 25° and ionic strength 0.50, plotted against $\sigma^+$ substituent constants. The benzaldehydes employed and the numerical values of the catalytic constants are listed in Table I.

Dehydration of the intermediate carbinolamine is the rate-determining step above pH 5. It is difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines from benzaldehydes and phenylhydrazine due to the strong interference absorption of the latter substance. Similar difficulties have been noted in attempts to determine the equilibrium constant for formation of the carbinolamine from ethyl pyruvate and phenylhydrazine.[5] However, with each of the benzaldehydes, the reaction is first-order in phenylhydrazine concentration over the concentration range of $5.0 \times 10^{-3}$ to $5.0 \times 10^{-2}$ *M*.

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[14] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1959).

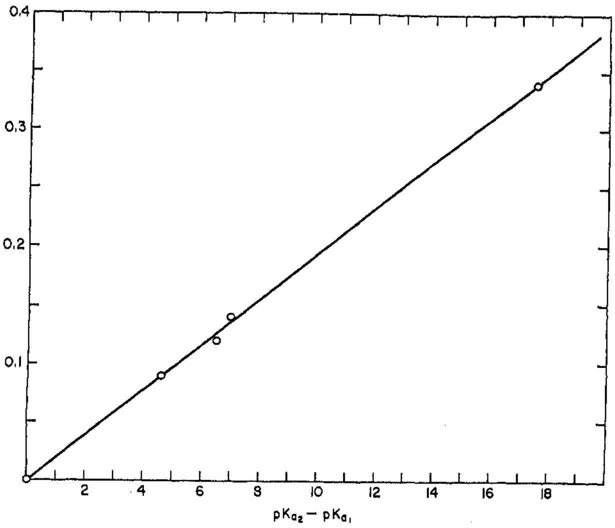


Figure 4.—Variation of $\rho^+$ values for the catalytic constants of several acids for the attack of phenylhydrazine on para-substituted benzaldehydes, in 20% ethanol at 25° and ionic strength 0.50, as a function of the $pK_a$ of the catalysts.

Consequently, all kinetic studies above pH 5 have been made employing phenylhydrazine concentrations lower than $5.0 \times 10^{-2}$ *M;* second-order rate constants could therefore be determined directly from observed rate constants and the concentration of phenylhydrazine free base.

The dehydration reaction for all the benzaldehydes is susceptible to specific acid catalysis from pH 5 to 9 (Figure 1). For *p*-chlorobenzaldehyde, benzaldehyde, and *p*-methoxybenzaldehyde, a pH-independent reaction is observed above pH 9 and for *p*-nitrobenzaldehyde both a pH-independent and a specific base-catalyzed reaction are observed (Figure 1). The appropriate rate constants are collected in Table V.

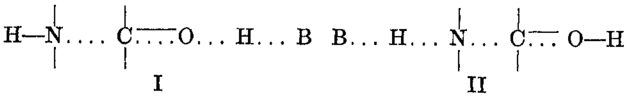
TABLE V

CATALYTIC CONSTANTS FOR THE HYDRATED PROTON, WATER, AND HYDROXIDE ION FOR THE DEHYDRATION OF CARBINOLAMINE INTERMEDIATES IN THE REACTION OF PHENYLHYDRAZINE WITH SEVERAL BENZALDEHYDES IN 20% ETHANOL AT 25° AND IONIC STRENGTH 0.50

| Benzaldehyde | $k_{H^+}$, $M^{-2}$ min$^{-1}$ | $k_{H_2O}$, $M^{-1}$ min$^{-1}$ | $k_{OH^-}$, $M^{-2}$ min$^{-1}$ |
|---|---|---|---|
| *p*-Nitrobenzaldehyde | $4.5 \times 10^8$ | 0.40 | $4.0 \times 10^2$ |
| *p*-Chlorobenzaldehyde | $3.0 \times 10^8$ | 0.44 | |
| Benzaldehyde | $2.4 \times 10^8$ | 0.25 | |
| *p*-Methoxybenzaldehyde | $7.0 \times 10^7$ | 0.088 | |
| *p*-Hydroxybenzaldehyde | $3.0 \times 10^7$ | | |

## Discussion

**A. Attack Reaction.**—Several arguments have been presented previously to the effect that general acid catalysis of the addition of nitrogen nucleophiles to carbonyl compounds occurs with true general acid catalysis (transition state I) rather than with specific acid–general base catalysis (transition state II).[3,4,6,8,15–17]



$\mathrm{H{-}N\ldots C\cdots O\ldots H\ldots B}$ I $\qquad \mathrm{B\ldots H\ldots N\ldots C\cdots O{-}H}$ II

Results obtained herein support this conclusion. In the first place a simple calculation based on the experimental third-order rate constant for the hydrated proton-catalyzed attack of phenylhydrazine on *p*-nitrobenzaldehyde (Table I) and the basicity of this aldehyde[18] reveal that the second-order rate constant for attack of the nucleophile on the protonated aldehyde is $9 \times 10^{15}\ M^{-1}\ \mathrm{min}^{-1}$ several orders of magnitude larger than rate constants for diffusion-controlled reactions in water.[6,19] Alternate routes to the formation of transition state II appear equally unreasonable as previously developed.[8] Thus, either transition state I must obtain or the reaction must proceed by a "single-encounter" mechanism. Variants of I in which proton transfer occurs through intervening water molecules and the like are, of course, not excluded.

In the second place, the variation of the values of $\rho^+$ with the acidity of the general acid catalyst (Figure 3) together with considerations concerning variation in transition state structure as function of reactivity[20–23] support transition state I. Specifically, one expects that with increasingly strong acid catalysts this transition state will be reached progressively earlier along the reaction coordinate, consistent with the observation of decreasing values of $\rho^+$ with increasing acid strength in the catalysts (Figure 3). In contrast, transition state II would predict the opposite since as the strength of the acid catalyst increases the basicity of the conjugate base necessarily decreases. One would expect the transition state to be reached later with the weaker general base catalyst and, hence, that the $\rho^+$ values would change in the opposite way. In general, both the magnitude and trend of the values of $\rho^+$ for corresponding reactions for semicarbazone and phenylhydrazone formation from benzaldehydes are similar[6] suggesting similar catalytic pathways. The observation that the rate constants for both water and the hydrated proton fall near the lines in the Brønsted plots constructed from the data for catalysis by carboxylic acids suggests that a common catalytic pathway is employed by all.

The variation in $\rho^+$ with $pK_a$ of the general acid catalysts can be treated quantitatively. Since the data may be correlated by both Hammett and Brønsted equations, it is easy to show that the following relationship should exist.[6,24]

$$\frac{pK_{a_2} - pK_{a_1}}{\rho_2^+ - \rho_1^+} = C_1 = \frac{\sigma_i}{\alpha_0 - \alpha_i} \tag{4}$$

Data in Table IV provide a test of former part of this equation which asserts that on changing the catalyst, change of $\rho^+$ is linearly related to the $pK_a$ of the acid employed as catalyst. Taking the data for the hydrated proton catalysis as standard, a plot of $\rho^+$ against $pK_a$ has been constructed (Figure 4). Clearly a satis-

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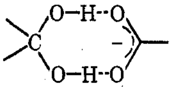
factory straight line is obtained. The slope of the line yields a value of $C_1$ of 50. This value of $C_1$ requires that the value of $\rho^+$ vary only slightly as a function of $pK_a$ in accord with the experimental observations in this work. Specifically, it is predicted that a change of 1.0 in $pK_a$ will cause only a change of 0.02 in $\rho^+$.

The observed values of $\alpha$, near 0.35, while small, are considerably greater than those observed for benzaldehyde semicarbazone and thiosemicarbazone formation[6,7] and are larger than expected on the basis of a relationship between $\alpha$ and the $pK_a$ of the nucleophilic reagent.[8] Why the value of $\alpha$ for phenylhydrazone formation should be so large is not completely clear. A very recent observation may, however, require some modification in interpretation of Brønsted exponents for general acid catalysis of carbonyl addition reactions. Specifically, the ratio of rate constants for addition of nucleophiles to benzaldehyde and benzaldehyde-*1-d* is near the theoretical upper limit requiring that C–N bond formation be essentially complete in the transition state.[25] Hence, proton transfer reactions involving the tetrahedral intermediates may be at least partially rate determining for these reactions.[26] Were proton transfer to the immediate adduct rate determining, the value of $\alpha$ would necessarily be zero. Perhaps the actual value observed is principally a reflection of the extent to which proton transfer is rate determining.

A particularly puzzling observation concerning addition of phenylhydrazine to benzaldehydes is the nonlinearity of plots of buffer concentration against rate constants when employing the *p*-nitro aldehyde as substrate (Figure 2). Similar observations have been made previously and reflect a transition to rate-determining carbinolamine dehydration.[6,7] As developed in the Experimental Section, correcting the observed rate constants in the present case to account for the importance of the rate of dehydration has little effect on these constants in the present case. Note specifically that the apparent limiting rate constant with increasing acetate buffer concentration shown in Figure 2 is about an order of magnitude less than that expected for rate-determining dehydration of the carbinolamine. Hence an alternative explanation must be found for this case.

**B. Carboxylate Inhibition of Phenylhydrazone Formation.**—Having eliminated one possible cause of carboxylate ion inhibition for phenylhydrazone formation from *p*-nitrobenzaldehyde, we are left with that one developed in the Results section: formation of an unreactive complex between substrate and inhibitor. In addition to accounting for the observed inhibition quantitatively, complex formation seems reasonable on the grounds that only the most electrophilic of the substrates experiences such inhibition and that the more nucleophilic carboxylate ions are the better inhibitors.

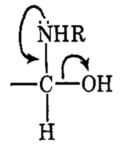
One difficulty with the concept of complex formation is the structure of that complex. Carboxylate ions are known to complex with hydrates of certain aliphatic aldehydes,[27] probably through hydrogen bond formation.



From available information concerning equilibrium constants for the addition of nucleophiles to benzaldehydes,[28] the possibility of direct addition of carboxylate ions to the *p*-nitrobenzaldehyde seems exceedingly remote. At any event, complexation, if it does occur, does not result in a detectable alteration in the ultraviolet absorption spectrum of the aldehyde.

**C. Carbinolamine Dehydration.**—The dehydration of the carbinolamines formed from the addition of phenylhydrazine to the substituted benzaldehydes is subject to strong acid catalysis and the rates are only slightly sensitive to the nature of polar substituents (Table V). In both regards, the results are typical for reactions of this type.[6,29–31]

The observation of pH-independent dehydration reactions appears to be the first direct detection of such a reaction for weakly basic amines. Several such reactions have been observed for the reverse reaction involving Schiff bases derived from strongly basic amines.[32,33] By analogy with the pathway for Schiff base hydrolysis, the pH-independent reaction must occur as follows.



By assuming a dissociation constant for the conjugate acid of the carbinolamine, protonated on oxygen, of $10^3$ *M*, the data in Table V permit one to calculate that the O-protonated carbinolamine expels water about $10^{12}$ times as rapidly as the neutral species expels hydroxide ion. If the acid-catalyzed and pH-independent reactions are viewed as involving general acid catalysis by the hydrated proton and water, respectively, then the ratio of rate constants is near $5 \times 10^{13}$ (correcting for the concentration of water in the solvent), fully consistent with the large values of $\alpha$ usually associated with carbinolamine dehydration.[7,32]

Base-catalyzed carbinolamine dehydration has been previously observed for semicarbazone and oxime formation.[31] Is it not surprising that such catalysis is most important for the *p*-nitrobenzaldehyde (Figure 1) since the electron-withdrawing capacity of the nitro group will diminish the capacity of the unshared pair on nitrogen to expel the leaving hydroxide group. Hence, removal, or partial removal, of the proton on nitrogen provides important additional driving force for the reaction and causes the base-catalyzed pathway to be important.

**Registry No.**—Benzaldehyde phenylhydrazone, 588-64-7; phenylhydrazine, 100-63-0; *p*-nitrobenzaldehyde, 555-16-8; *p*-chlorobenzaldehyde, 104-88-1; benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *p*-hydroxybenzaldehyde, 123-08-0.

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