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Mechanism and Catalysis for *o*-Hydroxyacetophenone Phenylhydrazone Formation[1]

Kaethy B. Alves, Marilene P. Bastos, and Luciano do Amaral*

Instituto de Química da Universidade de São Paulo, Caixa Postal 20.780, 01000 São Paulo, SP Brazil

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Acetophenone phenylhydrazone formation, like that of meta-/para-substituted benzaldehydes, occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamines from this substrate is subject to general acid–base catalysis by carboxylic acid–carboxylate buffers. 2′-Hydroxyacetophenone phenylhydrazone formation also occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of the carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamine from this substrate is subject to specific acid catalysis, but is not subject to detectable general acid–base catalysis by carboxylic acid–carboxylate buffers. It is proposed that this lack of general acid–base catalysis is due to internal hydrogen bond formation between the acidic hydrogen of the *o*-hydroxy substituent and the carbonyl group. The same was observed for carbinolamine formation from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones (substituent = nitro, cyano, chloro, and methyl). Rate constants for the hydrated proton catalysis and for the pH-independent reaction are well correlated by a dual Hammett substituent parameter treatment.

The rates of reaction of *o*-hydroxybenzaldehyde and the corresponding para isomer with a variety of nitrogen nucleophiles, including hydroxylamine, semicarbazide, *p*-toluidine, and phenylhydrazine, have been reported to exhibit ortho/para ratios considerably greater than unity.[2-5] This has been attributed to greater stabilization of the para- than the ortho-substituted benzaldehydes by substituents which donate electrons by resonance.[5]

A detailed study of the kinetics of phenylhydrazone formation from acetophenone and 2′-hydroxy-5′-substituted acetophenones was undertaken in order to examine the effect of ortho substituents capable of forming hydrogen bonds with the carbonyl oxygen of the acetophenone on reactivity toward nucleophiles.

Experimental Section

Materials. Acetophenone, 2′-hydroxyacetophenone, phenylhydrazine hydrochloride, and the carboxylic acids employed were obtained commercially and were either redistilled or recrystallized before use. *p*-Methyl-, *p*-chloro-, *p*-cyano-, and *p*-nitrophenyl acetates were prepared by the procedure of Bender and Nakamura.[6] 2′-Hydroxy-5′-methylacetophenone,[7] 2′-hydroxy-5′-chloroacetophenone,[8] 2′-hydroxy-5′-cyanoacetophenone,[8] and 2′-hydroxy-5′-nitroacetophenone[9] were prepared from the esters indicated above by procedures described in the literature. The acetophenone phenylhydrazones were prepared by the procedure of Vogel.[7]

p-Cyanophenyl acetate: mp 57–58 °C; NMR (60 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 7.47 (q, 4 H); IR (KBr) 2200, 1760, 1196, 840 cm^{-1}. Anal. Calcd: C, 67.08; H, 4.37; N, 8.65. Found: C, 66.40; H, 4.39; N, 8.58. 2′-Hydroxy-5′-cyanoacetophenone: mp 105–106 °C; NMR (60 MHz, $CDCl_3$) δ 2.68 (s, 3 H), 7.08 (d, 1 H), 7.75 (q, 1 H), 8.12 (d, 1 H), 12.7 (s, 1 H); IR (KBr) 2220, 1648, 1480, 1210, 840 cm^{-1}. Anal. Calcd: C, 67.08; H, 4.37; N, 8.70. Found: C, 66.77; H, 4.36; N, 8.75. 2′-Hydroxy-5′-chloroacetophenone phenylhydrazone: 174–175 °C; NMR (60 MHz, $(CD_3)_2SO$) δ 2.40 (s, 3 H), 6.60–7.80 (m, 8 H), 9.67 (s, 1 H), 12.8 (s, 1 H); IR (KBr) 3300, 1625 cm^{-1}. Anal. Calcd: C, 64.52; H, 4.99; N, 10.75. Found: C, 64.06; H, 5.28; N, 10.80. 2′-Hydroxy-5′-cyanoacetophenone phenylhydrazone: 192–193 °C; NMR (60 MHz, $(CD_3)_2SO$) δ 2.40 (s, 3 H), 6.60–7.80 (m, 8 H), 7.90 (d, 1 H), 9.60 (s, 1 H); IR 3325, 2225, 1615 cm^{-1}. Anal. Calcd: C, 71.87; H, 5.21; N, 16.72. Found: C, 71.08; H, 5.28; N, 16.53.

Kinetic measurements were carried out spectrophotometrically in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 with the aid of a Zeiss PMQ II spectrophotometer equipped with a cell through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the phenylhydrazone of acetophenone at 332 nm, of 2′-hydroxyacetophenone at 337 nm, of 2′-hydroxy-5′-methylacetophenone at 340 nm, of 2′-hydroxy-5′-chloroacetophenone at 342 nm, and of 2′-hydroxy-5′-nitroacetophenone at 345 nm up to pH 8 and at 450 nm in basic solution. The initial concentration of the acetophenones was 3.3×10^{-5} M, and 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.

As a result of the strong UV light absorption of phenylhydrazine, it was difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines. Similar difficulties have been noted in attempts to determine equilibrium constants for the formation of other phenylhydrazine carbinolamines.[10,11] With each of the acetophenones studied, the reaction is first-order in phenylhydrazine over the concentration range of 0.020 to 0.20 M, at pH 7. Consequently, all kinetic studies have been made employing phenylhydrazine concentrations lower than 0.20 M. Second-order rate constants could therefore be determined directly by dividing first-order rate constants by the concentration of phenylhydrazine free base. Catalytic third-order rate constants were evaluated from the slopes of plots of second-order rate constants against the concentration of catalyst.

Values of apparent pH were recorded with a Radiometer Model PHM 4d pH meter equipped with a glass electrode. Calculation of the concentration of phenylhydrazine free base and of undissociated carboxylic acid was made employing the Henderson–Hasselbalch equation and values of pK_a from ref 12.

pK_a Determination. The pK_a values of the 2′-hydroxy-5′-substituted acetophenones were measured in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 using a Zeiss PMQ II spectrophotometer. The effect of pH on the absorption of light was measured at the appropriate wavelength (Table I). The values of K_a were determined employing the equation $(E^- - E_t)/(E_t - E^\circ) = (H^+)/K_a$, where E^- is the absorption of the phenoxide, E° is the absorption of the phenol,

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Table I. Values of pK_a for Several 2′-Hydroxy-5′-substituted Acetophenones[a]

substituent	nm	slope	r	K_a	pK_a
NO_2	400	8.875×10^6	0.9991	1.127×10^{-7}	6.95
CN	350	5.447×10^7	0.9998	1.838×10^{-8}	7.74
Cl	370	3.503×10^9	0.9982	2.854×10^{-10}	9.55
H	364	2.544×10^{10}	0.9985	3.931×10^{-11}	10.40
CH_3	379	5.160×10^{10}	0.9989	1.937×10^{-11}	10.71

[a] In 20% aqueous ethanol at 25 °C and ionic strength 0.50.

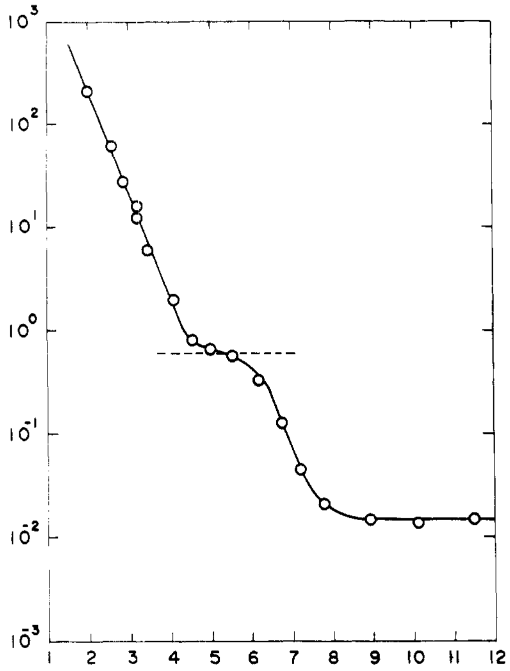


Figure 1. Logarithms of second-order rate constants for acetophenone phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH. Where necessary, the points were extrapolated to 0 buffer concentration. The broken line indicates the rate constant for the water-catalyzed process. Data have been taken from Table II.

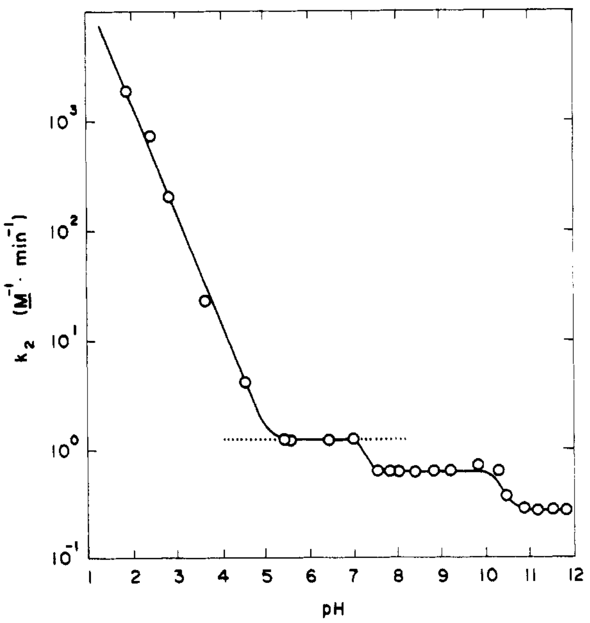


Figure 2. Logarithms of second-order rate constants for 2′-hydroxyacetophenone phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH. The dotted line indicates the rate constant for internal catalysis (see text). Data have been taken from Table II.

and E_t is the total absorption at the various pH values. Plots of $(E^- - E_t)/(E_t - E^0)$ vs. (H^+) yield the value of K_a (Table I).

Results

Acetophenone Phenylhydrazone Formation. Logarithms of second-order rate constants for the reaction of phenylhydrazine with acetophenone in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 are plotted as a function of pH in Figure 1. Where necessary, the second-order rate constants were extrapolated to 0 buffer concentration. The curve shows one break near pH 6 that must reflect the transition in rate-determining step from formation to dehydration of the carbinolamine intermediate.[10,12-16]

Second-order rate constants for acetophenone phenylhydrazone formation at pH 2.56 increased linear from 0.0113 to 0.0225 M^{-1} min^{-1} with an increase in cyanoacetate buffer concentration from 0.050 to 0.25 M. Buffer catalysis was also observed for chloroacetate, formate, and acetate. The nature of the catalysis, general acid or general base, was not defined.

2′-Hydroxyacetophenone Phenylhydrazone Formation. In Figure 2, logarithms of second-order rate constants for the reaction of phenylhydrazine with 2′-hydroxyacetophenone are plotted as a function of pH. The curve shows two breaks, one near pH 7 and the second near pH 10. The former must reflect the transition in rate-determining step, and the later, which occurs at the pK_a for the substrate, must reflect loss of the phenolic hydrogen of the substrate. Carbinolamine dehydration is presumably rate determining under quite basic conditions, although this point has not been carefully proved.

In the region of rate-determining carbinolamine formation (pH to 7), no catalysis by carboxylic acid–carboxylate buffers was observed, in contrast to the results for acetophenone itself.

2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation. In Figure 3, logarithms of second-order rate constants for the reaction of phenylhydrazine with 2′-hydroxy-5′-nitroacetophenone (I), 2′-hydroxy-5′-cyanoacetophenone (II), 2′-hydroxy-5′-chloroacetophenone (III), 2′-hydroxyacetophenone (V), and 2′-hydroxy-5′-methylacetophenone (VI) are plotted as a function of pH, in the pH range of 1 to 7. The curves show the pH-independent reaction and the acid-catalyzed carbinolamine formation as the rate-determining steps. For comparison, the curve obtained with acetophenone was included (IV).

In the region of rate-determining carbinolamine formation (pH 1 to 7), no catalysis by carboxylic acid–carboxylate buffers was observed for any of the 2′-hydroxy-5′-substituted acetophenones. Catalytic constants for the acid-catalyzed reaction (k_H) and the pH-independent one (k_O) have been evaluated from the data of Figure 3 and are collected in Table II.

Correlation Analysis of the log K_a Values of 2′-Hydroxy-5′-substituted Acetophenones. As is developed in detail below, the log K_a values of the 2′-hydroxy-5′-substituted acetophenones, as well as the rate constants for the hydrated proton catalysis and for the pH-independent reaction for

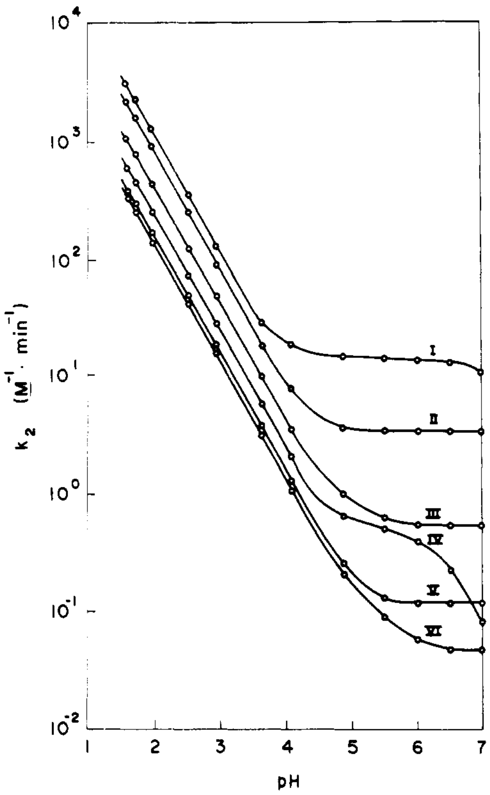
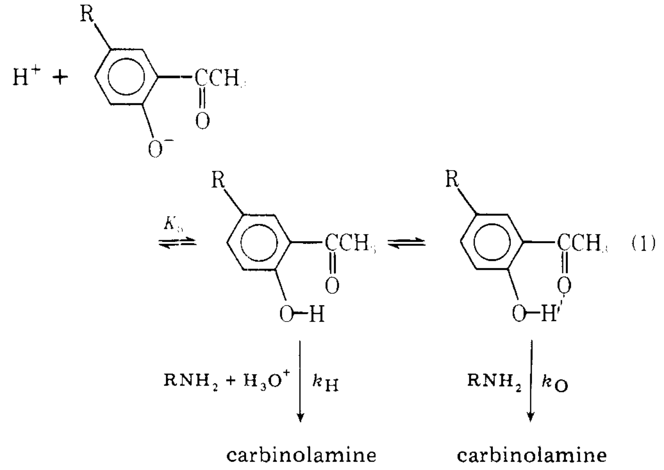


Figure 3. Logarithms of second-order rate constants for acetophenone and 2′-hydroxy-5′-substituted acetophenone phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH: (I) 2′-hydroxy-5′-nitroacetophenone; (II) 2′-hydroxy-5′-cyanoacetophenone; (III) 2′-hydroxy-5′-chloroacetophenone; (IV) acetopheone; (V) 2′-hydroxyacetophenone; and (VI) 2′-hydroxy-5′-methylacetophenone. The lines for the 2′-hydroxy-5′-substituted acetophenones are theoretical ones based on $k_2 = k_H(H_3O^+) + k_O$ and data from Table II.

phenylhydrazone formation from these compounds, are well correlated by dual Hammett substituent parameter treatment.

The K_a values of the 2′-hydroxy-5′-substituted acetophenones are influenced by the presence of the substituent R and by the presence of the acetyl group in the benzene ring (see eq 1 and Discussion).



The log K_a values were correlated by the modified Hammett equation 2. Multiple least-squares analysis with a computer program yielded eq 3. It was then possible to calculate the dual Hammett substituent parameters for the correlation analysis of the log K_a values of the 2′-hydroxy-5′-substituted acetophenones (Table III).

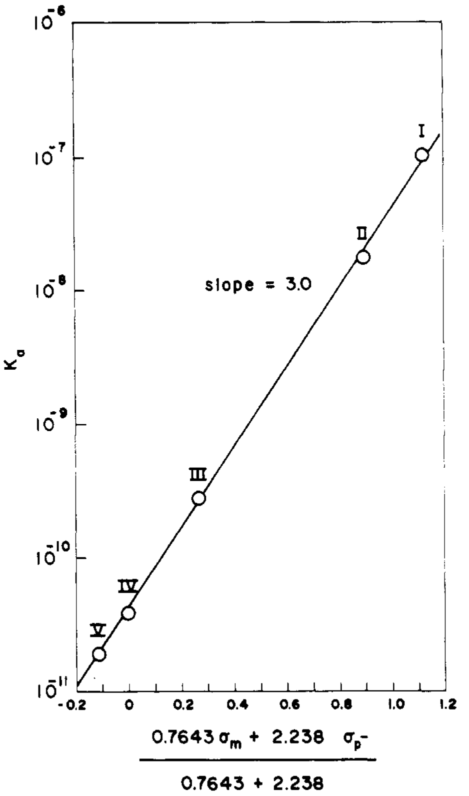


Figure 4. Logarithms of K_a of 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against $(0.7643\sigma_m + 2.2338\sigma_p^-)/(0.7643 + 2.2338)$: (I) 2′-hydroxy-5′-nitroacetophenone; (II) 2′-hydroxy-5′-cyanoacetophenone; (III) 2′-hydroxy-5′-chloroacetophenone; (IV) 2′-hydroxyacetophenone; and (V) 2′-hydroxy-5′-methylacetophenone. Data have been taken from Tables I and III.

Table II. Catalytic Constants for the Hydronium Ion (k_H) and pH-Independent Reaction (k_O) for the Addition of Phenylhydrazine to Several Acetophenones[a]

compd	registry no.	k_H, M^{-2} min^{-1}	k_O, M^{-1} min^{-1}
2′-hydroxy-5′-nitroacetophenone	1450-76-6	1.1×10^5	1.3×10^1
2′-hydroxy-5′-cyanoacetophenone	35794-84-4	8.0×10^4	3.6×10^0
2′-hydroxy-5′-chloroacetophenone	1450-74-4	4.5×10^4	5.4×10^{-1}
acetophenone	98-86-2	2.3×10^4	6.2×10^{-1}
2′-hydroxyacetophenone	118-93-4	1.5×10^4	1.1×10^{-1}
2′-hydroxy-5′-methylacetophenone	1450-72-2	1.3×10^4	4.9×10^{-2}

[a] In 20% aqueous ethanol at 25 °C and ionic strength 0.50.

$$\log K_a = \log K_a^{\circ} + \sigma_m\rho_m + \sigma_p^-\rho_p^- \qquad (2)$$

$$\log K_a = -10.383 + 0.7643\sigma_m + 2.238\sigma_p^- \qquad (3)$$

In Figure 4, values of log K_a of the 2′-hydroxy-5′-substituted acetophenones (from Table I) are plotted as a function of the appropriate dual Hammett substituent parameters (from Table III). The points fall on a good straight line. By least-squares analysis, the value of the slope of the line is 3.0, the correlation coefficient $r = 0.9993$, and the standard deviation divided by the root mean square (SD/RMS) is 0.00509.

Correlation of log K_a values of 2′-hydroxy-5′-substituted acetophenones with any other set of substituent constants gives inferior correlation coefficients and/or higher SD/RMS ratios.

Table III. Values of σ for Some Substituents

group	σ_m[a]	σ_p[a]	σ_p^- [a]	$\frac{0.7643\sigma_m + 2.238\sigma_p^-}{0.7643 + 2.238}$	$\frac{1.401\sigma_m - 0.1850\sigma_p}{1.401 - 0.1850}$	$\frac{0.7419\sigma_m + 1.869\sigma_p}{0.7419 + 1.869}$
NO_2	0.71	0.78	1.27	1.12	0.70	0.76
CN	0.61	0.67	1.00	0.90	0.60	0.65
Cl	0.37	0.24	0.24	0.27	0.38	0.28
H	0	0	0	0	0	0
CH_3	−0.07	−0.13	−0.13	−0.11	−0.06	−0.11

[a] From ref 17.

Correlation Analysis of the log k_H Values for 2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation. The rate constants for the hydrated proton catalysis (k_H) for the formation of the carbinolamines from 2′-hydroxy-5′-substituted acetophenones and phenylhydrazine are influenced by the presence of the substituent R and by the presence of the hydroxy group in the benzene ring (see Discussion).

The logarithms of the k_H values were correlated by the modified Hammett equation 4. Multiple least-squares analysis with a computer program yielded eq 5. It was then possible to calculate the dual Hammett substituent parameters for the correlation analysis of the log k_H values for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (Table III).

$$\log k_H = \log k_H^\circ + \sigma_m\rho_m + \sigma_p\rho_p \qquad (4)$$

$$\log k_H = 4.187 + 1.401\sigma_m - 0.1850\sigma_p \qquad (5)$$

In Figure 5, values of log k_H for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted as a function of the appropriate dual Hammett substituent parameters (from Table III). The points fall in a good straight line. By least-squares analysis, the value of the slope of the line is 1.2, $r = 0.9997$, and SD/RMS = 0.00175.

Correlation of log k_H with any other set of substituent constants gives inferior correlation coefficients and higher SD/RMS ratios.

Correlation Analysis of the log k_O Values for 2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation. The rate constants for the pH-independent reaction (k_O) for the formation of the carbinolamines from 2′-hydroxy-5′-substituted acetophenones and phenylhydrazine are influenced by the presence of the substituents R and by the hydrogen bond between the phenolic group and the carbonyl group (see eq 1 and Discussion).

The logarithms of k_O values were correlated by the modified Hammett equation 6. Multiple least-squares analysis by a computer program yielded eq 7. It was then possible to calculate the dual Hammett substituent parameters for the correlation analysis of log k_O values for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (Table III).

$$\log k_O = \log k_O^\circ + \sigma_m\rho_m + \sigma_p\rho_p \qquad (6)$$

$$\log k_O = -0.9968 + 0.7419\sigma_m + 1.869\sigma_p \qquad (7)$$

In Figure 6, values of log k_O for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted as a function of the appropriate dual Hammett substituent parameters (from Table III). The points fall on a good straight line. By least-squares analysis, the value of the slope of the line is 2.6, $r = 0.9906$, and SD/RMS = 0.106.

Correlation of log k_O with any other set of substituent constants gives inferior correlation coefficients and higher values of SD/RMS.

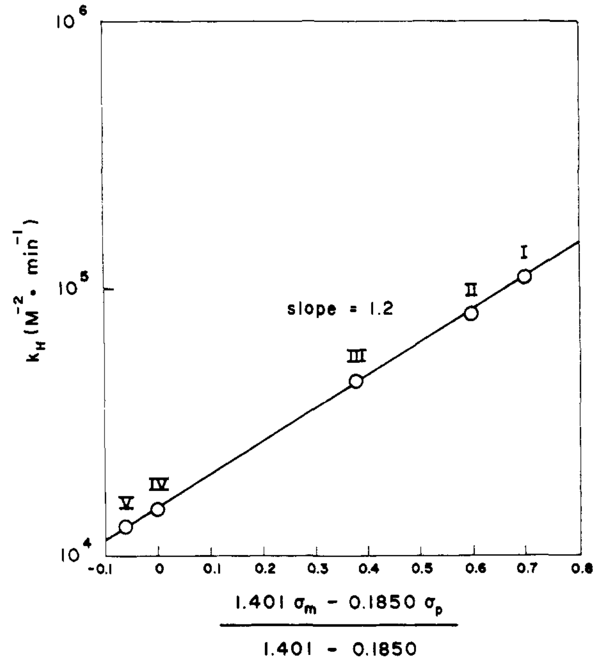


Figure 5. Logarithms of the catalytic constants for the hydrated proton (k_H) for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against $(1.401\sigma_m - 0.1850\sigma_p)/(1.401 - 0.1850)$. Data have been taken from Tables II and III.

Correlation Analysis of the log k_H Values for 2′-Hydroxy-5′-substituted Acetophenone Phenylhydrazone Formation and the log K_a Values of 2′-Hydroxy-5′-substituted Acetophenones. In Figure 7, values of the logarithms of the catalytic constants for the hydrated proton (k_H) for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted against the pK_a values of the corresponding 2′-hydroxy-5′-substituted acetophenones (from Table I). The points fall on a single straight line, whose slope is 0.25 ($r = 0.9766$). Since the catalyst is the same (hydronium ion) for all of the reactions, this correlation is not a Brönsted plot. This plot correlates the simultaneous electronic effect of the substituent in the 5′ position of the benzene ring on the carbonyl group and on the phenolic hydroxy group.

In Figure 8, values of the logarithms of the pH-independent rate constants (k_O) for the formation of the carbinolamines from phenylhydrazine and the 2′-hydroxy-5′-substituted acetophenones (from Table II) are plotted against the pK_a values of the corresponding 2′-hydroxy-5′-substituted acetophenones (from Table I). The points fall on a single straight line, whose slope is 0.60 ($r = 0.9923$).

Discussion

The reaction of phenylhydrazine with acetophenone occurs with rate-determining carbinolamine formation under slightly acidic conditions. This step is subject to both specific catalysis

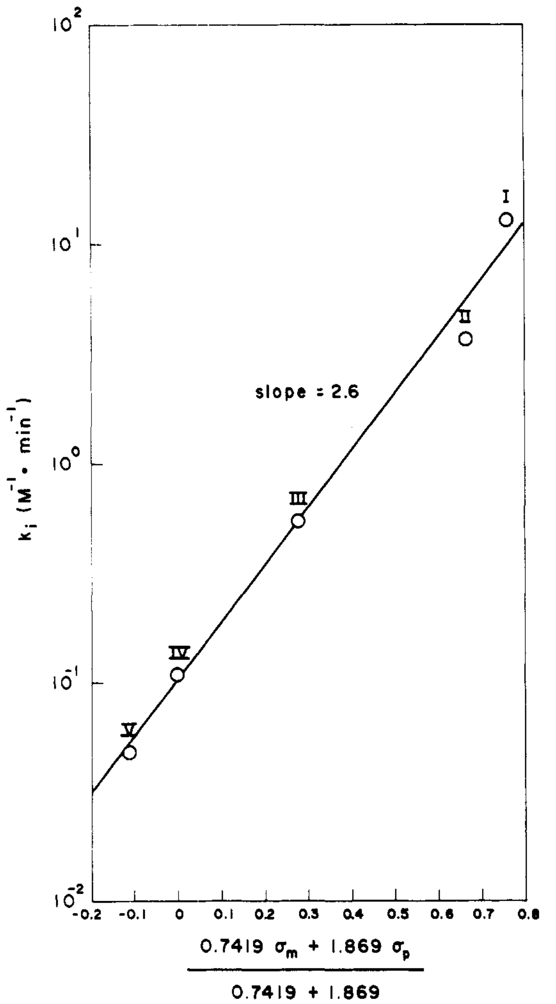
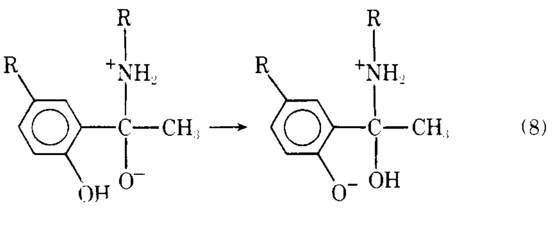


Figure 6. Logarithms of the internal catalytic constants (k_O) for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against $(0.7419\sigma_m + 1.869\sigma_p)/(0.7419 + 1.869)$: (I) 2′-hydroxy-5′-nitroacetophenone; (II) 2′-hydroxy-5′-cyanoacetophenone; (III) 2′-hydroxy-5′-chloroacetophenone; (IV) 2′-hydroxyacetophenone; and (V) 2′-hydroxy-5′-methylacetophenone. Data have been taken from Tables II and III.

(hydronium ion) and buffer catalysis by carboxylic acid–carboxylate buffers. Under basic conditions, dehydration of the carbinolamine becomes rate determining. The behavior is similar to that observed in the reaction of phenylhydrazine and meta-/para-substituted benzaldehydes.[10] As expected, acetophenone is less reactive than benzaldehyde.[10]

The reaction of phenylhydrazine with 2′-hydroxyacetophenone occurs with rate-determining carbinolamine formation below pH 7. This step shows specific acid catalysis and pH-independent reaction, but not detectable buffer catalysis by carboxylic acid–carboxylate buffers.

The pH-independent reaction for the 2′-hydroxy substrates could be (i) trapping of the zwitterionic intermediate by -OH (eq 8), (ii) concerted internal protonization by -OH (eq 9), or (iii) rate-determining proton switch (eq 10). Our data suggests that the last mechanism is probably wrong, but it does not distinguish between the first two.



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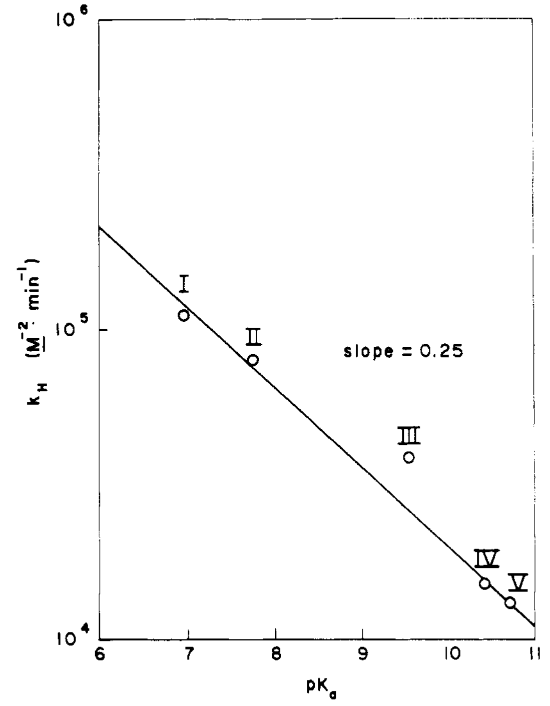
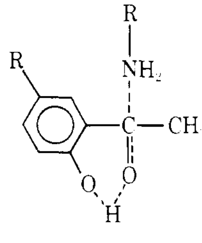


Figure 7. Logarithms of catalytic constants for the hydrated proton for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against their respective pK_a values: (I) nitro; (II) cyano; (III) chloro; (IV) unsubstituted; and (V) methyl. Data have been taken from Tables I and II.



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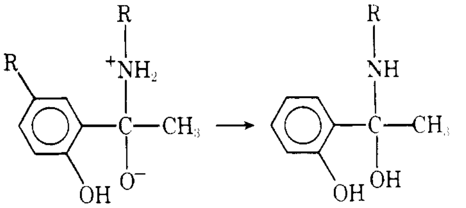


(10)

The plot of values of the logarithms of the pH-independent rate constants (k_O) for the formation of the carbinolamines from phenylhydrazine and 2′-hydroxy-5′-substituted acetophenones (Figure 8) may reflect the simultaneous electronic effect of the substituents in the 5′ position of the benzene ring upon the carbonyl and phenolic groups, a true Brönsted-type free energy relationship between the logarithms of the internal catalytic constants and the pK_a's of the phenols, or a combination of these effects. We prefer the last explanation. The simultaneous effect gives rise to a slope of 0.25. The α Brönsted plot value measured for the formation of the carbinolamine from phenylhydrazine and several carbonyl compounds[10,12,15,16] is always 0.35. The slope of 0.60 in Figure 8 is the total of both effects (0.25 + 0.35 = 0.60). This would suggest that both reactions are concerted, not stepwise.[19]

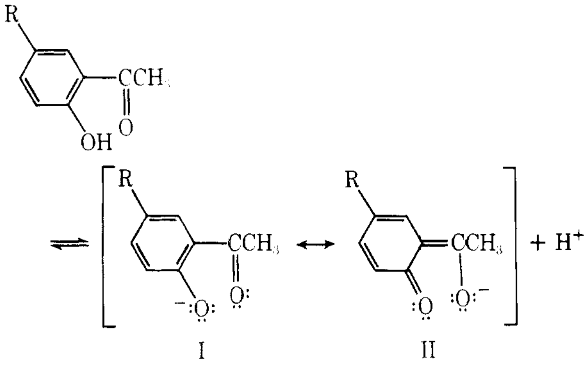
It is well known that in 2′-hydroxyacetophenone there is an internal hydrogen bond between the hydrogen of the phenolic group and the oxygen of the carbonyl group.[18] The best explanation for the pH-independent reaction is that the reaction is subject to a concerted internal protonization by the intramolecular hydrogen bond between the hydrogen of the hydroxylic group on the ortho position and the oxygen of the carbonyl group.[20-22] The rate law for this reaction is then $k_2 = k_H(H_3O^+) + k_O$. The internal hydrogen bond explains the observation that the formation of the carbinolamine from phenylhydrazine and 2′-hydroxyacetophenone occurs without detectable generated acid catalysis by carboxylic acids.

The specific acid catalysis is observed because there is an equilibrium between the hydrogen-bonded form of the 2′-hydroxyacetophenone (cyclic form) and the form without the hydrogen bond (open form), as shown in eq 1. The open form reacts with hydronium ion catalysis.

In comparison to the case of acetophenone, the mechanism of dehydration of the carbinolamine derived from the reaction of phenylhydrazine and 2′-hydroxyacetophenone, observed as rate determining in pH above 7, is less straightforward. Several forms of the carbinolamine with different kinds of internal hydrogen bonding may be involved.

We have limited, therefore, the study of the addition of phenylhydrazine to the 2′-hydroxy-5′-substituted acetophenones to pH 1–7, a region in which the formation of the carbinolamine is rate determining.

The R substituents in the 5′ position of the ring, meta to the carbonyl group and para to the hydroxy group, exert an electronic effect on both groups in a way that affects both the ionization of the phenolic group and the rate of the carbinolamine formation. The pK_a values of the 2′-hydroxy-5′-substituted acetophenones are influenced by the presence of the R substituents and by the presence of the acetyl group in the benzene ring. The ionization is given by eq 11, where it is shown that the acetyl group contributes to the stabilization of the phenoxide ion.



(11)

Electron-withdrawing R substituents increase the K_a value of the hydroxylic group by decreasing its electronic density and by decreasing the electronic density of the carbonyl group, thus stabilizing form II. Electron-donating R substituents exert an opposite effect.

The log K_a values were then correlated by a modified Hammett equation (eq 2) that gives rise to the values in eq 3. The largest contribution is given by σ_p^- values, but a minor contribution is observed from the σ_m substituent constants.

The influence of the substituents R and the hydroxy group on the rate of formation of the carbinolamines will now be discussed.

The k_H values for the formation of the carbinolamines from phenylhydrazine and the 2′-hydroxy-5′-substituted acetophenones are influenced by the presence of the R substituents and by the presence of the hydroxy group in the benzene. The protonization of the carbonyl group is increased by the hydroxy group (eq 12).

If R is an electron-withdrawing substituent, the rate of the carbinolamine formation increases due to the decrease in electronic density of the carbonyl group. On the other hand, electron-withdrawing R substituents decrease the rate of carbinolamine formation by decreasing the electronic density of the hydroxy group, thus destabilizing form II′. The electron-donating R substituents exert an opposite effect.

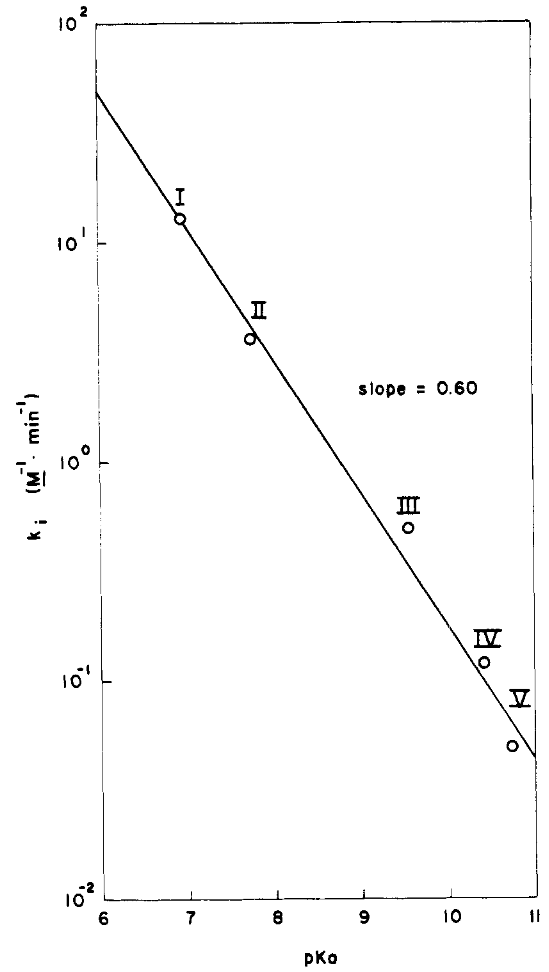
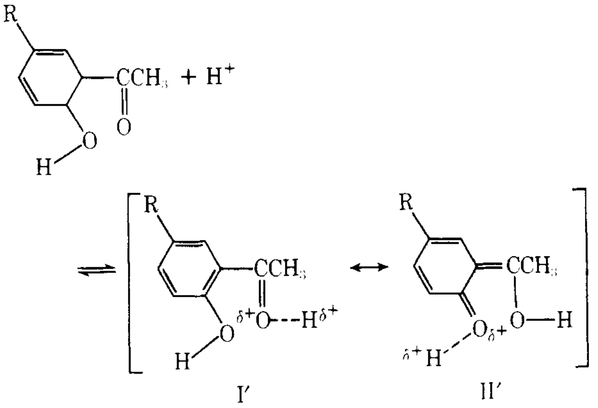


Figure 8. Logarithms of the internal catalytic constants for the formation of the carbinolamines from phenylhydrazine and several 2′-hydroxy-5′-substituted acetophenones in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted against their respective pK_a values: (I) nitro; (II) cyano; (III) chloro; (IV) unsubstituted; and (V) methyl. Data have been taken from Tables I and II.



(12)

The log k_H values were then correlated by a modified Hammett equation (eq 4) that gives rise to the values of eq 5. As a consequence of the electronic effect of R on the carbonyl group in the meta position, the contribution of σ_m is positive; as a consequence of the electronic effect of R on the hydroxy group in the para position, the contribution of σ_p is negative. The largest contribution is given by σ_m values.

With respect to the internal catalysis, the electron-withdrawing R substituents increase the rate of the carbinolamine formation by decreasing the electronic density of the carbonyl group and by decreasing the electronic density of the hydroxy group. This makes the phenolic group a stronger acid, and consequently leads to a strong hydrogen bond. The electron-donating R substituents exert an opposite effect.

The log k_O values were then correlated by a modified Hammett equation (eq 6) that gives rise to the values in eq 7. The values show a positive contribution of σ_m and a positive contribution of σ_p. The contribution of σ_p is higher than the contribution of σ_m.

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Registry No.—Phenylhydrazine, 100-63-0; *p*-cyanophenyl acetate, 13031-41-9; 2′-hydroxy-5′-chloroacetophenone phenylhydrazone, 67338-35-6; 2′-hydroxy-5′-cyanoacetophenone phenylhydrazone, 67338-36-7.

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Catalysis in Aromatic Nucleophilic Substitution. 3.[1] Reactions of Piperidine with 2-Methoxy-3-nitrothiophene and 2-Methoxy-5-nitrothiophene in Methanol

D. Spinelli* and G. Consiglio

Cattedra di Chimica Organica, Faculty of Pharmacy, University of Bologna, Via Zanolini 3, Bologna 40126, Italy

R. Noto

Institute of Organic Chemistry, University of Palermo, Via Archirafi 20, Palermo 90123, Italy

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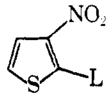
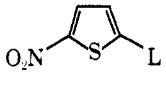
The kinetics of piperidino substitution of 2-methoxy-3-nitrothiophene (If) and of 2-methoxy-5-nitrothiophene (IIf) have been studied in methanol as a function of amine concentration. The reaction of IIf is second order overall, whereas that of If is base catalyzed. Kinetic data are presented which show that sodium methoxide (added or deriving from the reaction of piperidine with methanol) is the only effective catalyst. The complex kinetic system resulting from the competition, at high sodium methoxide concentrations, between the reactions of If respectively with piperidine and with sodium methoxide (Meisenheimer-type adduct formation) has been computer analyzed and the rate coefficients for the single reactions have been estimated. The whole of the data obtained shows that acid catalysis of leaving-group departure by the conjugated acid of piperidine does not occur or is insignificant. The special role of the activating nitro group is discussed.

A recent study[1] of piperidino substitutions of some 2-L-3-nitro- (Ia–e) and 2-L-5-nitrothiophenes (IIa–e), in benzene and in methanol, has shown that only the reactions of compounds IId,e in benzene are piperidine catalyzed due to the poor nucleofugicity of *p*-nitrophenoxy and phenylsulfonyl groups in this solvent; while in compounds Ia–e the *o*-nitro group can assist the intermediate decomposition in both solvents.[2]

For piperidino substitutions in methanol, we now wish to report straightforward second-order kinetic behavior for 2-methoxy-5-nitrothiophene (IIf) but base catalysis for 2-methoxy-3-nitrothiophene (If). The role played by the position of activating nitro group (hyper-ortho or quasi-para) in determining the occurrence of base catalysis will be discussed.



I



II

a, L = Cl
b, L = Br
c, L = I
d, L = $OC_6H_4NO_2$-*p*
e, L = SO_2Ph
f, L = OMe

Results and Discussion

Products. Compounds If and IIf gave the corresponding substitution products with piperidine in high yields (>95%) as shown by TLC and/or UV–visible spectral analysis of the reaction mixtures at infinity.

Reaction of IIf with Piperidine. The apparent second-order kinetic constant, k_A, for the piperidino substitution of IIf in methanol at 20 °C (Table I) is independent of the initial piperidine concentration over a tenfold change.

There can be little doubt that this reaction is second order overall, first order both in substrate and in nucleophile, and that there is no measurable catalysis by the amine acting as a base. This corresponds to the situation where $k_A = k_1$ (see below).

Reaction of If with Piperidine. Items 1–6, 8–10, 12, 14, and 16 in Table II show that k_A increases in a curvilinear