Ortho Effect in Benzaldehyde Phenylhydrazone Formation[1]

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Ortho-substituted benzaldehyde phenylhydrazone formation, like that for para-substituted benzaldehydes, occurs with rate-determining carbinolamine formation under slightly acidic conditions and with rate-determining dehydration of carbinolamine under basic conditions. The addition of phenylhydrazine to form carbinolamines from these substrates is subject to general acid catalysis by carboxylic acids: Brønsted α is 0.3–0.4. Rate constants have been measured for the separate steps in the reaction of phenylhydrazine with several ortho- and para-substituted benzaldehydes. Rate constants for hydrated proton catalysis for para-substituted benzaldehyde phenylhydrazone formation are well correlated by a dual Hammett substituent parameter treatment: $\log k_H = \log k^\circ_H + \rho_I\sigma_I + \rho_R{}^+\sigma_R{}^+$. ρ_R is slightly greater than ρ_I, indicating that the resonance effect of substituents is somewhat more important than the inductive effect for this reaction. Rate constants for hydrated proton catalysis for ortho-substituted benzaldehyde phenylhydrazone formation are also well correlated by a dual Hammett substituent parameter treatment: $\log k_H = \log k^\circ_H + \rho_I\sigma_I + \rho_R\sigma_R$. In this case ρ_I is much larger than ρ_R, indicating that the inductive effect of the substituents is much more important than the resonance one for this reaction. These results account for the order of the ortho/para rate ratios for the benzaldehydes studied.

Structural modifications of a reactant molecule may, in principle, influence the rate or equilibrium constants of a reaction through polar, resonance, or steric effects. When a substituent is introduced at a point remote from the reaction center, only the operation of polar effects usually need be considered and quite detailed understanding of the influence of structure upon reactivity is possible. Linear free-energy relationships, notably the Hammett equation, are a very important tool for such structure–reactivity correlations. In contrast, when the structural modification is close to the reaction center, as in α-substituted aliphatic systems and ortho-substituted aromatic systems, the simultaneous occurrence of both steric and polar effects complicates the application of linear free-energy relationships.

Steric phenomena have long been believed to play a major role in the peculiar effects of ortho substituents on reactivity. Steric effects of various kinds, including steric hindrance to solvation or to the approach of the reagent, have been invoked. Little progress was made in this regard until 1952, when Taft[2] developed a procedure for separating the polar, resonance, and steric effects. Considerable use has been made of Taft's analysis and of the substituent parameters derived therefore, particularly those for aliphatic systems. On the other hand, the Taft's parameters for ortho substituents have been successfully applied to relatively few systems.

The idea that *para*-substituted systems provide a basis for interpreting the ortho effect was proposed by Kindler.[3] Recently, Charton compiled and analyzed a vast amount of data on the ortho effect.[4] His work is based on the separation of the electronic effect of a substituent X into inductive and resonance contributions. Some of his findings and conclusions are very remarkable. Thus, he found that, for ortho effect, both the inductive and resonance contributions of X are important; at the same time E_s values of ortho substituents have little to do with steric parameters.

The mechanism of the addition of nitrogen nucleophilic reagents to carbonyl compounds has been the subject of a great number of studies in recent years.[5-8] The rates of reaction of ortho-substituted benzaldehydes and the corresponding para isomers 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.[9-12] This has been attributed to greater stabilization of the para- than ortho-substituted benzaldehydes by substituents which donate electrons by resonance.[12]

A detailed study of the kinetics of phenylhydrazone formation from ortho- and para-substituted benzaldehydes was undertaken in order to obtain further information about the magnitude and mechanism of ortho-substituent effects.

Experimental Section

Materials. All reagents employed were obtained commercially and, with 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% aqueous ethanol were prepared just prior to use to avoid esterification.

Kinetic measurements were carried out spectrophotometrically at 25.0 °C with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder, through which water from a thermostated bath was continuously circulated. Reaction kinetics were monitored by observing the appearance of the phenylhydrazone at the appropriate wavelength. The initial concentration of the benzaldehydes 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 equilibrium constants for formation of carbinolamines. Similar difficulties have been noted in attempts to determine equilibrium constants for formation of other phenylhydrazine carbinolamines.[6,13] With each of the benzaldehydes studied, the reaction is first-order in phenylhydrazine over the concentration range 0.020 to 0.20 M, at pH 7. This result requires that the equilibrium constant for carbinolamine formation not be greater than about 3 M^{-1}, consistent with the fact that this equilibrium constant for addition of 4-sulfonylphenylhydrazine to *p*-chlorobenzaldehyde is 1.8 M^{-1}.[7] Consequently, all kinetic studies have been made employing phyenylhydazine concentrations lower than 0.20 M. Second-order rate constants could, therefore, be determined directly by dividing first-order rate constants by the concentrations of phenylhydrazine free base.

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.[8] In the present case, such a correction introduces no appreciable changes in the rate constants for carbinolamine formation, a consequence of large ratios between the third-order rate constants for acid-catalyzed carbinolamine formation and dehydration.

Catalytic third-order rate constants were evaluated from slopes of plots of second-order rate constants against the concentration of the catalyst. Calculation of the concentrations of phenylhydrazine free base and undissociated carboxylic acids were made employing the Henderson–Hasselbalch equation. The pK_a for phenylhydrazine was determined to be 5.26 (see below) and those for carboxylic acids were taken from ref 8.

pK_a Determination. The pK_a of phenylhydrazinium ion (5.26 ± 0.010) (Table I, supplementary material) was measured at 25.0 °C in 20% aqueous ethanol and ionic strength 0.50, maintained with KCl, by careful partial neutralization of eight samples of the hydrochloride

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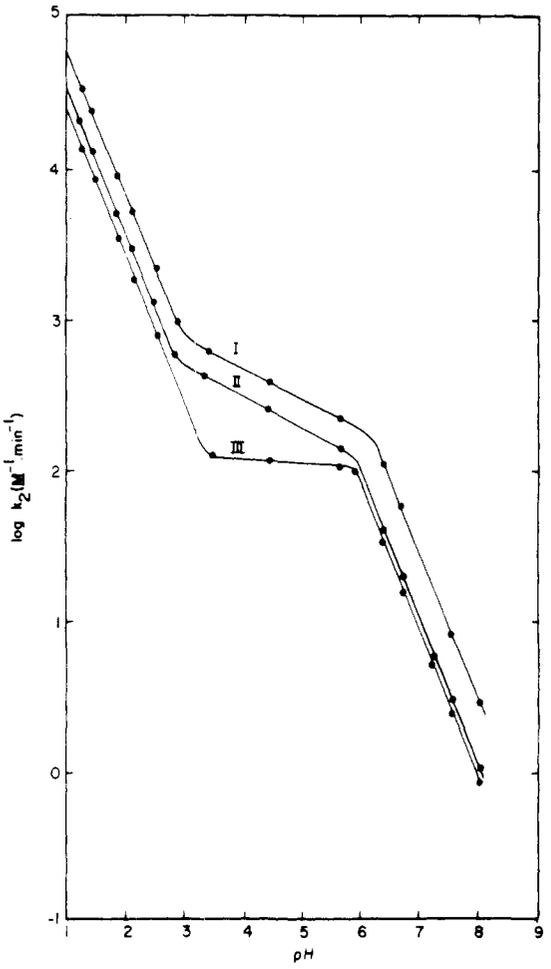


Figure 1. Logarithms of second-order rate constants for para-substituted benzaldehyde phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH: I, *p*-bromobenzaldehyde; II, *p*-fluorobenzaldehyde; III, *p*-methylbenzaldehyde.

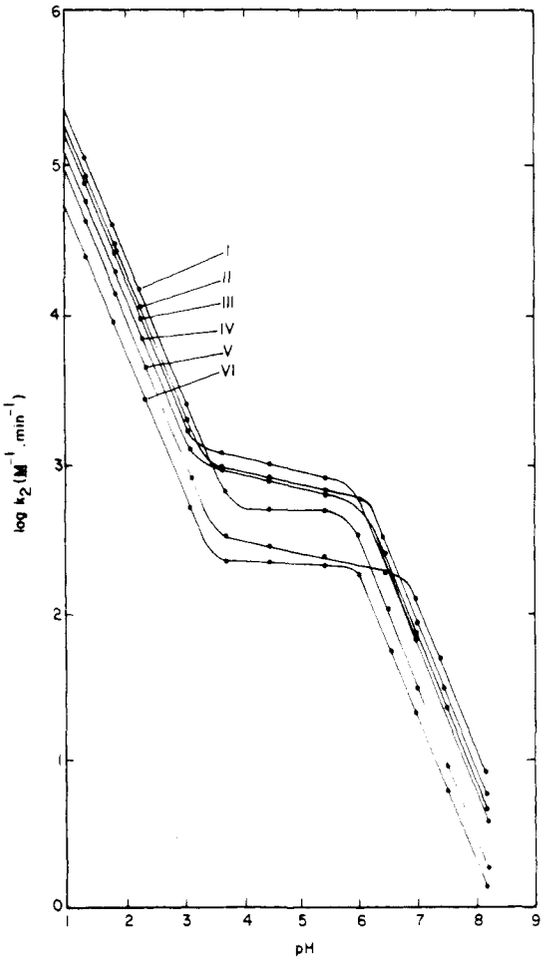


Figure 2. Logarithms of second-order rate constants for ortho-substituted benzaldehyde phenylhydrazone formation in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as a function of pH: I, *o*-nitrobenzaldehyde; II, *o*-chlorobenzaldehyde; III, *o*-bromobenzaldehyde; IV, *o*-fluorbenzaldehyde; V, *o*-methoxybenzaldehyde; VI, *o*-methylbenzaldehyde.

to different extents with known amounts of standard potassium hydroxide solution. The pH values of these solutions were measured with a Corning Model 12 pH meter, equipped with a glass electrode. The glass electrode was initially calibrated with blank solution of the same ionic strength containing 0.0100 M hydrochloric acid whose pH was taken as 2.00. Under such conditions the measured values of pH refer to hydronium ion concentration rather than to hydronium ion activities. The pK_a was obtained from measured values of pH employing the Henderson–Hasselbach equation.

Results

In Figures 1 and 2 the logarithms of second-order rate constants for the reaction of phenylhydrazine with various ortho- and para-substituted benzaldehydes in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 are plotted as a function of pH. Where necessary the second-order rate constants were extrapolated to zero buffer concentration.

Table II. Slopes of Plots of Second-Order Rate Constants for the Formation of the Carbinolamine Intermediate from Phenylhydrazine and *o*-Nitrobenzaldehyde [b] Against the Concentration of Chloroacetic Acid–Chloroacetate Buffers [a]

pH	% of buffer in basic form	concn range, M	slope ClAcOH	slope $ClAcO^-$
2.28	20	0.01–0.15	2.2×10^5	9.0×10^5
2.62	35	0.01–0.15	1.2×10^5	2.5×10^5
3.46	80	0.01–0.15	7.5×10^4	2.1×10^4

[a] The slopes have the units of M^{-2} min^{-1}. [b] 20% aqueous ethanol at 25.0 °C and ionic strength 0.50.

In the region of rate-determining formation of the carbinolamine, second-order rate constants are sensitive functions of the nature and concentration of the carboxylic acid–carboxylate buffer employed to maintain constant pH.

With the exception of *o*-nitrobenzaldehyde, the buffer catalysis for benzaldehyde phenylhydrazone formation proved straightforward. Studies of buffer catalysis demonstrated that, as usual, it is of the general acid type.[5,14] *o*-Nitrobenzaldehyde exhibits unique behavior in its reaction with phenylhydrazine. Plots of the second-order rate constants for this reaction as a function of the concentration of chloroacetic acid–chloroacetate buffers at various degrees of neutralization yield straight lines whose slopes are collected in Table II. 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, as observed for the formation of *p*-nitrobenzaldehyde phenylhydrazone.[13]

The catalytic rate constants derived from the data in Figures 1 and 2 and from studies of buffer catalysis are collected in Table III. Catalytic constants for the reactions of phenylhydrazine and *p*- and *o*-nitrobenzaldehydes have been corrected for the hydration of the aldehydes, using data in the

Table III. Catalytic Constants of Several Acids, Expressed in M^{-2} min^{-1}, for the Formation of the Carbinolamine from the Reaction of Phenylhydrazine and Several ortho-para-Substituted Benzaldehydes at 25.0 °C in 20% Aqueous Ethanol and Ionic Strength 0.50

catalyst	registry no.	pK_a	p-OCH_3[a,b]	p-F[c]	p-Cl[a,d]	p-Br[c]	p-CH_3[f]	H[a,g]	p-NO_2[a,h]
H_3O^+	13968-08-6	−1.74	1.6×10^5	5.6×10^5	1.2×10^6	1.0×10^6	4.0×10^5	9.0×10^5	3.7×10^6
$CNCH_2CO_2H$	372-09-8	2.46	1.7×10^4	6.6×10^4	7.6×10^4	1.4×10^5	4.3×10^4	9.5×10^4	4.9×10^5
$ClCH_2CO_2H$	79-11-8	2.88	1.0×10^4	3.7×10^4	6.6×10^4	1.1×10^5	3.4×10^4	5.9×10^4	4.0×10^5
HCO_2H	64-18-6	3.63	6.5×10^3	3.0×10^4	4.0×10^4	5.4×10^4	2.5×10^4	5.0×10^4	1.6×10^5
$BrCH_2CH_2CO_2H$	590-92-1	4.10	4.7×10^3	1.9×10^4	3.7×10^4	3.0×10^4	1.8×10^4	5.4×10^4	1.1×10^5
CH_3CO_2H	64-19-7	4.74	2.2×10^3	1.3×10^4	1.7×10^4	2.7×10^4	1.2×10^4	1.5×10^4	6.9×10^4
catalyst		pK_a	o-OCH_3[i]	o-F[j]	o-Cl[k]	o-Br[l]	o-CH_3[m]		o-NO_2[n]
H_3^+O		−1.74	1.4×10^6	1.9×10^6	2.6×10^6	2.4×10^6	7.9×10^5		3.6×10^6
$CNCH_2CO_2H$		2.46	1.0×10^5	1.8×10^5	2.9×10^5	1.9×10^5	5.9×10^4		
$ClCH_2CO_2H$		2.88	7.2×10^4	1.5×10^5	2.0×10^5	1.5×10^5	4.0×10^4		
HCO_2H		3.63	4.4×10^4	8.0×10^4	8.9×10^4	7.9×10^4	2.0×10^4		
$BrCH_2CH_2CO_2H$		4.10	2.0×10^4	4.7×10^4	6.0×10^4	5.3×10^4	1.8×10^4		
CH_3CO_2H		4.74	1.4×10^4	2.6×10^4	3.5×10^4	3.3×10^4	1.0×10^4		

[a] From ref 6; the values for p-nitrobenzaldehyde have been corrected for the hydration of the aldehyde.[12] [b] Registry no. 123-11-5. [c] Registry no. 459-57-4. [d] Registry no. 104-88-1. [e] Registry no. 1122-91-4. [f] Registry no. 104-87-0. [g] Registry no. 100-52-7. [h] Registry no. 555-16-8. [i] Registry no. 135-02-4. [j] Registry no. 446-52-6. [k] Registry no. 89-98-5. [l] Registry no. 6630-33-7. [m] Registry no. 529-20-4. [n] Registry no. 552-89-6.

Table IV. Brønsted α Values for Catalysis by Carboxylic Acids for the Formation of Carbinolamines from the Addition of Phenylhydrazine to Several Ortho- and Para-Substituted Benzaldehydes at 25 0 °C in 20% Aqueous Ethanol and Ionic Strength 0.50[a]

benzaldehyde	α	correlation coefficient
p-NO_2	0.39	0.994
p-Br	0.34	0.980
p-Cl	0.28	0.988
p-F	0.29	0.981
p-CH_3	0.31	0.974
p-OCH_3	0.38	0.996
o-Br	0.35	0.999
o-Cl	0.41	0.999
o-F	0.38	0.995
o-CH_3	0.33	0.990
o-OCH_3	0.35	0.980

mean 0.34, stand dev 0.04

[a] Values of catalytic constants are taken from Table III.

literature.[15,16] Catalytic constants for the carboxylic acids are well correlated by the Brønsted catalysis law. Least-squares treatment of the data yields the values of α collected in Table IV. The α values are the same, within experimental error, for formation of the carbinolamine from phenylhydrazine and the para- or the ortho-substituted benzaldehydes, which suggests a single mechanism for carbinolamine formation from both sets of benzaldehydes.

Values of the catalytic constants for the hydrated proton are plotted against the σ^+ substituent constants.[17] A good correlation is obtained, yielding a ρ^+ value of 0.88 ($r = 0.9906$); nearly the same value has previously been determined for a more limited number of substrates.[13] The catalytic constants are better correlated by σ^+ than by σ substituent constants, 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.[18]

The dissection of σ constants into their inductive (σ_I) and resonance (σ_R) components provides two new scales of great theoretical interest.[17] The σ^+ constants were also broken into σ_I and σ_R^+. Pertinent values are collected in Table V (supplementary material).

For the formation of carbinolamines from phenylhydrazine and the para-substituted benzaldehydes we correlated the logarithms of the catalytic constants for the hydrated proton by the following equation:

$$\log k_H = \log k_H^0 + \rho_I\sigma_I + \rho_R^+\sigma_R^+ \quad (1)$$

The data from Tables III and V have been fitted to eq 1 by least-squares analysis employing a computer and yielded the following result:

$$\log k_H = 5.92 + 0.820\sigma_I + 0.928\sigma_R^+ \quad (r = 0.990)$$

This equation reveals the relative contributions of the inductive and resonance effects on carbinolamine formation exerted by a substituent in the para position. One sees that the resonance effect is slightly more important than the inductive one. Rate constants for phenylhydrazone formation from para-substituted benzaldehydes under conditions of rate-determining carbinolamine formation catalyzed by other acid species (Table III) were fitted to the same equation. Although the quantitative relationship of the ρ_I and ρ_R^+ constants varied, as expected since the number of data points is limited, the relative qualitative importance of the two was corroborated.

For the formation of carbinolamines from phenylhydrazine and the ortho-substituted benzaldehydes, in accordance with considerations of Charton,[4] we correlated the logarithms of the catalytic constants for the hydrated proton with the following equations:

$$\log k_H = \log k_H^0 + \rho_I\sigma_I + \rho_R\sigma_R \quad (2)$$

$$\log k_H = \log k_H^0 + \rho_I\sigma_I + \rho_R^0\sigma_R^0 \quad (3)$$

$$\log k_H = \log k_H^0 + \rho_I\sigma_I + \rho_R^+\sigma_R^+ \quad (4)$$

The data from Tables III and V have been fitted to eq 2, 3, and 4 by least-squares analysis employing a computer and yield respectively the following results.

$$\log k_H = 5.94 + 0.055\sigma_I + 0.0720\sigma_R \quad (r = 0.998)$$

$$\log k_H = 5.95 + 0.963\sigma_I + 0.0741\sigma_R^0 \quad (r = 0.997)$$

$$\log k_H = 5.96 + 0.964\sigma_I + 0.0475\sigma_R^+ \quad (r = 0.998)$$

These results show that the effect of substituents in the ortho position of the benzene ring is largely inductive. Since the contribution of the resonance effect is small, the choice of σ_R substituent constants is not important.

Rate constants for ortho-substituted benzaldehyde phenylhydrazone formation catalyzed by other acids (Table III)

were also fitted to eq 2. In each case, a good fit was obtained. Moreover, in each case the importance of the inductive effect, as measured by ρ_I, proved greater than that of the resonance effect, as measured by ρ_R. This observation accords with the conclusion based on the data for catalysis by the hydrated proton.

To correlate the logarithms of the catalytic rate constants for the hydrated proton for the formation of carbinolamines from phenylhydrazine and the ortho-substituted benzaldehydes, it was not necessary to introduce in eq 2, 3, or 4 a term to account for steric effects.

We correlated, therefore, the logarithms of the catalytic rate constants for the hydrated proton for ortho-substituted benzaldehyde phenylhydrazone formation by the following Hammett equation, that takes into account only the inductive effect:

$$\log k_H = \log k_H^0 + \rho_I \sigma_I \quad (5)$$

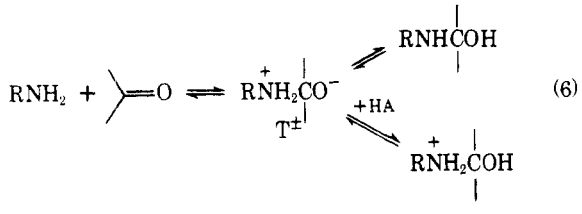
The data from Tables III and V have been fitted to eq 5 by least-squares analysis to yield the following result:

$$\log k_H = 5.94 + 0.972\sigma_I \quad (r = 0.996)$$

An explanation for the observation that the substituent in the ortho position of the benzene ring exert almost only an inductive effect is the steric inhibition of resonance between the carbonyl group and the benzene ring.[19]

Discussion

Plots of logarithms of second-order rate constants for phenylhydrazone formation from ortho- and para-substituted benzaldehydes against pH exhibit a single break down to pH 1 (Figures 1 and 2). These data strongly suggests a single change in rate-determining step over the pH range studied.[5,14] The acid-catalyzed reaction observed under alkaline conditions almost certainly reflects rate-determining carbinolamine dehydration.[5] The pH-independent and acid-catalyzed reactions observed under more acidic conditions most probably reflect trapping of a dipolar addition intermediate by proton transfer;[14] as justified above



(6)

Although the pH–rate profiles shown in Figures 1 and 2 do not permit a clear distinction between a stepwise and a concerted mechanism for carbinolamine formation,[7] comparison with related data strongly suggests that the former alternative is correct. For example, the addition of 4-sulfonylphenylhydrazine, conjugate acid pK_a 4.9, and methoxyamine, conjugate acid pK_a 4.73, to *p*-chlorobenzaldehyde occurs by a stepwise mechanism.[7] It follows that addition of the slightly more basic phenylhydrazine to aldehydes of similar reactivity should also occur in a stepwise fashion. Moreover, addition of methoxyamine to *p*-methoxybenzaldehyde is also stepwise;[7] consequently addition of phenylhydrazine to even quite unreactive benzaldehydes should be stepwise. Finally, data for phenylhydrazine and *p*-chlorobenzaldehyde (Table III) fall on a line which correlates logarithms of third-order rate constants for hydrated proton-catalyzed carbinolamine formation and the quantity $(0.8pK_a + 0.2 \log K_{ad})$ which is established by amines whose mechanism is known to be stepwise.[7] For this correlation we have employed a value of 2 M^{-1} for K_{ad}, consistent with data indicated above. We conclude that the mechanism of carbinolamine formation for the reactions studied here is very probably stepwise. It follows that there should be a second break in the pH–rate profile under conditions more acidic than those employed in this investigation.

Table VI. Ortho/Para Ratios for the Hydronium-Catalyzed Reaction of Formation of the Carbinolamine from Phenylhydrazine and Several Benzaldehydes in 20% Aqueous Ethanol at 25.0 °C and Ionic Strength 0.50

substituent	k_H(ortho)/k_H(para)[a]	substituent	k_H(ortho)/k_H(para)[a]
MeO	6.6 ± 1.5	CH_3	1.1 ± 0.5
F	2.9 ± 0.7	H	1.0
Cl	2.5 ± 0.8	NO_2	0.97
Br	1.6 ± 0.4		

[a] The values are averages of ratios calculated for all acid catalysts employed (Table III).

For the acid-catalyzed carbinolamine, rate constants increase with increasing electron withdrawal by polar substituents in the benzaldehyde moiety, in accord with previous observations.[5,13,14,18] The value of ρ^+ for the para-substituted substrates, 0.88, is close to that measured for acid-catalyzed carbinolamine formation from benzaldehydes and semicarbazide, 0.71.[18] The observed value of ρ^+ for phenylhydrazone formation is consistent with rate-determining trapping of $T^{\pm}$ by proton transfer.

Values of the Brønsted exponent for general acid catalysis of addition of phenylhydrazine to both ortho- and para-substituted benzaldehydes, 0.3–0.4, although somewhat larger than those previously observed for closely related reactions, are small enough to be consistent with the mechanism indicated in eq 6.

If acid-catalyzed carbinolamine formation reflects trapping of $T^{\pm}$ by proton transfer (eq 6), it follows that structure–reactivity correlations should be largely independent of the nature of the catalyzing acid. As noted above, this is the case, within the error of the experimental results, for the influence of the polar substituents on the rate constants. This conclusion should also hold for ortho/para rate ratios; that is, one would expect these ratios to be independent of the nature of the acid which traps the dipolar addition intermediate, $T^{\pm}$. Values of k_{ortho}/k_{para} have been calculated from the data provided in Table III for all catalyzing acids. Although there is some scatter in the ratios, as expected, they are largely independent of the catalyzing acid for all ortho/para pairs studied, in accord with expectations based on the above argument. The average values of k_{ortho}/k_{para} are collected in Table VI, together with standard deviations. The value obtained for the methoxy derivatives is close to that previously measured for acid-catalyzed benzaldehyde semicarbazone formation, 5.6.[12]

In a thorough analysis of ortho/para rate ratios for benzaldehyde semicarbazone formation, Wolfenden and Jencks concluded that the principal underlying cause was preferential stabilization of the para-substituted benzaldehydes by substituents which donate electrons by resonance that is, electron donation by resonance appears to be more important from the para than from the ortho position.[12] The results obtained in this investigation accord with this conclusion. First, the observation that resonance effects, as reflected in values of ρ_R^+, are at least as important as inductive effects, ρ_I, for determining reactivities of para substrates but much less important for determining reactivities of ortho substrates provides strong evidence for this argument. Second, on this basis, one might expect that log k_{ortho}/k_{para} would be at least qualitatively correlated by the σ_R^+ substituent constants. This expectation is borne out. The data points collected in Table VI fall on a reasonably straight line when plotted against σ_R^+; the slope

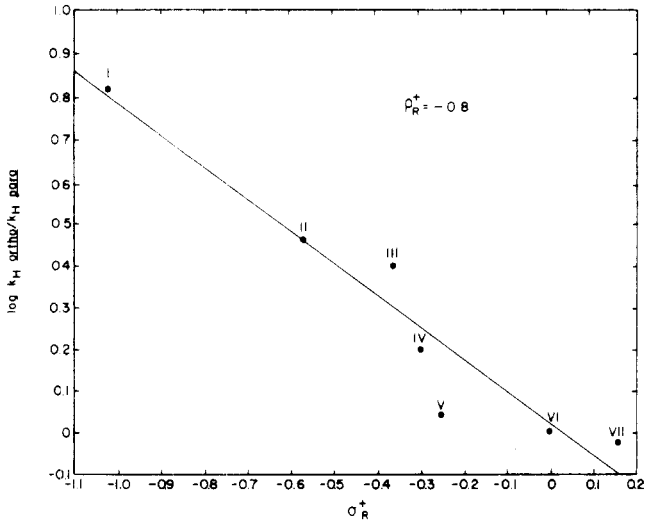


Figure 3. Logarithms of ortho/para ratios for the hydronium-catalyzed reaction of formation of carbinolamine from phenylhydrazine and several benzaldehydes, in 20% aqueous ethanol at 25.0 °C and ionic strength 0.50 plotted as function of σ_R^+ (I, methoxy; II, fluor; III, chloro; IV, bromo; V, methyl; VI, hydrogen; VII, nitro). Data have been taken from Tables V and VI.

is approximately −0.8, a value which emphasizes the importance of electron donation by resonance in decreasing the reactivity of para isomers relative to ortho ones (Figure 3).

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Registry No.—Phenylhydrazinium ion, 55668-06-9; phenylhydrazine, 100-63-0.

Supplementary Material Available: Table I, determinations of the acidity constant data for phenylhydrazinium ion, and Table V, values of Hammett substituent constants used in this work (2 pages). Ordering information is given on any current masthead page.

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Aspects of Tautomerism. 7. Study of Keto Participation in Alkaline Hydrolysis of Normal Esters of γ-Keto Acids[1]

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Study of the alkaline hydrolysis of a number of variously substituted normal *o*-benzoylbenzoic esters has been reported. Although carbonyl-assisted hydrolysis is the general rule, in compounds containing strongly electron-donating groups, the ester function is directly attacked. The cause of rate enhancement in carbonyl-assisted hydrolysis and in greater detail the case of 6-substituted derivatives are discussed. It is shown that the carbonyl-assisted hydrolyses are characterized by decreased sensitivity to leaving-group structure. The implications of this result are pointed out.

In the past decade or so, a number of examples of intramolecular catalysis in basic hydrolysis of carboxylic acid derivatives have been encountered.[2-16] It has been found that γ-keto and δ-keto functions enhance the rate of alkaline hydrolysis. These rate enhancements vary over a wide range, and values up to 10^5 times have been recorded.[5] Diverse explanations have been put forward by the authors for the observed effects (see below).

The present investigation is concerned with hydrolysis of normal methyl *o*-benzoylbenzoates with various substituents in both of the rings. The kinetics of saponification have been studied with a view to understanding (a) the causes of rate enhancements and (b) the influence of leaving-group structure on the rates of carbonyl-assisted basic hydrolysis.

Results and Discussion

The rate constants for the alkaline hydrolysis of "A" ring substituted *o*-benzoylbenzoates (cf. Scheme I) in 70% aqueous acetone are given in Table I. A good linear correlation exists between log *k* and Hammett substituent parameters (Figure 1). The ρ value is 2.22 (γ = 0.998). This value is almost identical with that for the alkaline hydrolysis of meta- and para-substituted methyl benzoates (ρ = 2.2).[7] If the base was reacting directly at the methoxycarbonyl group, values should have been comparable to the alkaline hydrolysis of pseudo esters, i.e., 0.56, and lactones, 0.64,[1] and the dissociation constants of A ring substituted *o*-benzoylbenzoic acids, viz., 0.6 (in 80% w/w 2-methoxyethanol–water).[7] It is clear that there is substantial transmission of polar effects to the reaction center. This observation is rather an expected one and fully corroborates the work of Bowden and Taylor.[7] The case of 4′-*N*,*N*-dimethylamino substituent is, however, untypical, as reflected in a large positive deviation from the Hammett plot (Figure 1). Clearly, this compound reacts by a mechanism

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