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The Effect of *o*-Substituents on Benzaldehyde Semicarbazone Formation¹

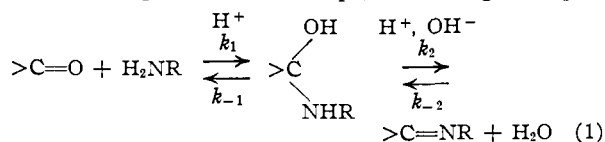
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Rate and equilibrium constants have been measured for the separate steps in the reaction of semicarbazide with benzaldehyde and ten of its *o*- and *p*-substituted derivatives. Differences in the rate and equilibrium constants for semicarbazone formation parallel differences in the extent of semicarbazide addition compound formation, for which unexpectedly high *ortho:para* ratios fall in the order MeO > HO ~ Cl > H > NO₂. The rate-enhancing effects of *o*-substitution cannot readily be explained by steric, inductive or hydrogen bonding effects. It is concluded that the results constitute strong evidence in favor of greater stabilization of *p*- than of *o*-substituted benzaldehydes by substituents which donate electrons by resonance. The basicities of benzaldehyde semicarbazones have been determined spectrophotometrically. The *pK_a* values of their conjugate acids fall near -1.1 and are insensitive to substituent effects, suggesting that protonation occurs on the terminal carboxamide group. The *pH* dependence of the apparent equilibrium constants for benzaldehyde semicarbazone formation agrees with the spectrophotometrically determined *pK* value.

Introduction

The reactions of methoxy- and hydroxybenzaldehydes with a variety of nitrogen bases, including semicarbazide, hydroxylamine, phenylhydrazine and *p*-toluidine, have been reported to exhibit *ortho:para* rate ratios considerably greater than 1,²⁻⁴ and it has been suggested that the rate-accelerating effect of these *o*-substituents is due to hydrogen bonding between the carbon-bound hydrogen of the -CHO group and the oxygen atom of the substituent.² Semicarbazone formation takes place in two steps, according to eq. 1



in which the first step is rate-determining at acidic *pH* and the dehydration step is rate-determining at neutral and alkaline *pH*.^{5a,b} A more detailed study of the effects of *o*-substituents on the separate steps of semicarbazone formation was undertaken in order to obtain further information about the magnitude and mechanism of *o*-substituent effects and because of a general interest in mechanisms of rate accelerations of reactions in aqueous solution.

Experimental

Materials.—Substituted benzaldehydes, with the exception of *o*-nitrobenzaldehyde, were obtained commercially and either redistilled under nitrogen at reduced pressure or twice recrystallized. *o*-Nitrobenzaldehyde was prepared by the method of Tsang, Wood and Johnson⁶ from *o*-nitrotoluene. The light yellow solid so obtained (m.p. 44°, uncor.)⁶ may be converted to colorless needles (m.p. 41°, uncor.)⁷ by recrystallization from water. The two forms have identical infrared spectra in chloroform.

Semicarbazide hydrochloride and hydroxylamine hydrochloride were twice recrystallized from 75% ethanol and neutralized with KOH just before use. Glass-distilled water

and ethanol were used throughout, the former being made 10⁻⁴ *M* in ethylenediaminetetraacetic acid.

Methods.—Kinetic measurements and measurements of equilibrium constants in 25% ethanol (25 ml. of ethanol per 100 ml. of solution) were made on a Zeiss model PMQ II spectrophotometer. Temperature was maintained at 25.0 ± 0.1° with a thermostated cuvette compartment. The *pH* values reported are the apparent *pH* values in 25% ethanol at 25°, obtained with the glass electrode of a Radiometer model 4 *pH* meter.

Calculated values for the concentration of free semicarbazide and free hydroxylamine are based on measured apparent *pK'* values of 3.65 for semicarbazide and 6.12 for hydroxylamine in 25% ethanol at ionic strength 0.32. The apparent *pK'* values for the hydroxybenzaldehydes are 7.84 for salicylaldehyde and 8.66 for *p*-hydroxybenzaldehyde, measured spectrophotometrically at ionic strength 0.10 in 25% ethanol at 380 and 285 m μ , respectively. No reaction was found to occur between the hydroxybenzaldehydes and semicarbazide under alkaline conditions, indicating that the phenolate anions are unreactive, as previously shown for the saponification of ethyl hydroxybenzoates.⁸ In calculating rate and equilibrium constants for the reaction of these aldehydes near neutrality, a small correction was made for their ionization.

Rate measurements were carried out as previously described,^{5a,b} with the concentration of attacking base in such excess that pseudo first-order kinetics were obtained. All reaction kinetics were measured in 25% ethanol at 25° at an ionic strength of 0.32, maintained by the addition of KCl. The presence of ethanol made possible the inclusion in the series of the water-insoluble nitrobenzaldehydes. Potassium phosphate buffers, 0.01 *M*, were used for the measurement of rates near neutrality; 0.01 *M* potassium carbonate and citrate-phosphate buffers were used at higher and lower *pH*, respectively. Buffer effects at this concentration were shown to be negligible. Dilute solutions of HCl and KOH were employed in regions of extreme acidity and basicity. At least ten determinations of over-all rate were made in duplicate over a wide range of *pH* values, as illustrated in Fig. 1. Rates for specific acid-catalyzed addition in dilute HCl were corrected for general acid catalysis by the conjugate acid of semicarbazide by extrapolation of second-order rate constants to zero semicarbazide concentration. Rate measurements were made at the absorption maximum of the semicarbazone or oxime formed.

Equilibrium constants for the addition of nitrogen bases to benzaldehyde in 25% ethanol at 25° were measured spectrophotometrically as previously described.^{5a,b} Addition compound formation was measured by the initial decrease in optical density at the aldehyde absorption maximum produced by addition of various concentrations of nitrogen base to the aldehyde at neutrality. At least seven determinations of the extent of addition compound formation at different semicarbazide or hydroxylamine concentrations were made for each aldehyde in at least two experiments, yielding an average value for *K₁* with a mean deviation of less than 4%. Over-all equilibrium constants for semicarbazone formation, *K_{ov}*, were obtained in 0.1 *M* HCl in 25% ethanol at 25° by measuring the change in optical den-

(1) Supported by grants from the National Cancer Institute of the National Institutes of Health (Grant C-3975) and from the National Science Foundation.

(2) G. Vavon and P. Montheard, *Bull. soc. chim. France*, **7**, 551 (1940).

(3) D. G. Knorre and N. M. Emanuel, *Doklady Akad. Nauk S.S.-S.R.*, **91**, 1163 (1953) (*C. A.*, **49**, 12936 (1955)).

(4) O. Bloch-Chaudé, *Compt. rend.*, **239**, 804 (1954).

(5) (a) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959), (b) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

(6) S. M. Tsang, E. H. Wood and J. R. Johnson, in "Organic Syntheses," Coll. Vol. III, ed. E. C. Horning, *et al.*, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 841.

(7) G. Bruni and A. Callegari, *Gazz. chim. ital.*, **34** [2], 196 (1904).

(8) L. Pekkarinen and B. Tommila, *Acta Chem. Scand.*, **13**, 1019 (1959).

TABLE I
 RATE AND EQUILIBRIUM CONSTANTS FOR SEMICARBAZONE FORMATION IN 25% ETHANOL AT 25°

X	$k_{1H}^+ \times 10^{-5}$, l ² . mole ⁻¹ min. ⁻¹	K_1 , l. mole ⁻¹	$k_{2H}^+ \times 10^{-7}$, l. mole ⁻¹ min. ⁻¹ ^a	k_{2OH}^- , l. mole ⁻¹ min. ⁻¹ ^b	$K_2 \times 10^{-3}$ ^c	$K_{ov} \times 10^{-6}$, l. mole ⁻¹	$k_{ov} \times 10^{-7}$, l ² . mole ⁻² min. ⁻¹ ^d	λ_{max} , m μ	μ Semi- carbazone
H	0.47	1.32 ^e	0.82 ^e		5.2	6.9	1.08	243	279
<i>o</i> -MeO	1.48	1.67	2.84	29.5	4.9	8.2	4.75	254	276
<i>p</i> -MeO	0.262	0.34 ^e	1.25	11.8	4.5	1.5	0.43	284	288
<i>o</i> -OH		.33	3.10		13.7	4.5	1.03	253	278
<i>p</i> -OH		.073	6.30		15.5	1.1	0.46	284	286
<i>o</i> -Me		1.05	1.42		6.7	7.0	1.49	253	280
<i>p</i> -Me		0.62 ^e	1.49		5.5	3.4	0.92	253	281
<i>o</i> -Cl		19.0	0.102		1.2	23.3	1.94	253	283
<i>p</i> -Cl		4.14 ^e	.207		2.5	10.5	0.86	259	285
<i>o</i> -NO ₂		27.1	.019		2.8	75	.52	257	260
<i>p</i> -NO ₂		40.1 ^e	.024		2.1	83	.96	268	329
Hammett's ρ		1.81	-1.74		-0.17	1.64	0.07		

^a $k_{2H}^+ = k_{obs}/(H^+)$ (fraction as addition compound). ^b $k_{2OH}^- = k_{obs}/(OH^-)$ (fraction as addition compound). ^c $K_2 = K_{ov}/K_1$. ^d $k_{ov} = K_1 k_{2H}^+$ in dilute solution. ^e Values from ref. 5b.

sity at the semicarbazone absorption maximum produced by adding various concentrations of semicarbazide hydrochloride to each aldehyde. The equilibrium constants were calculated from the formula $K_{ov} = \alpha/[1-\alpha][RNH_2]$, in which α is the fraction of aldehyde converted to semicarbazone, and the nitrogen base is present in great excess. At this acidity (apparent pH 1.10), equilibrium is rapidly achieved and no appreciable protonation of benzaldehyde semicarbazone occurs (see below).

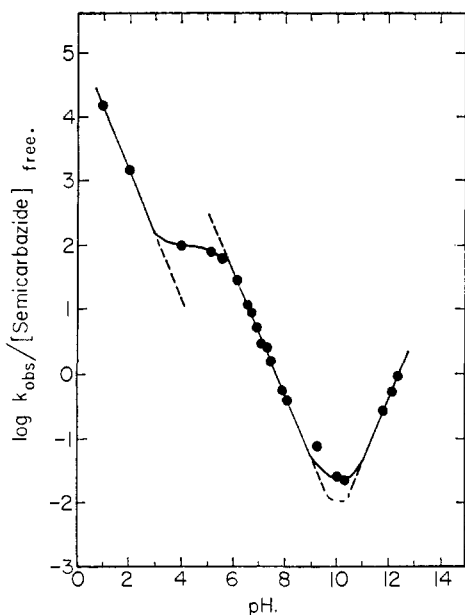


Fig. 1.—Dependence on apparent pH of the rate of α -methoxybenzaldehyde semicarbazone formation in 25% ethanol at 25°. The break in the curve in the acid region represents the shift from rate-determining dehydration to rate-determining semicarbazide attack; the dashed lines are calculated from the rate constants in Table I.

The pK' values of benzaldehyde semicarbazones in aqueous solution were determined with a Cary model 14 recording spectrophotometer by measuring the effect of various concentrations of hydrochloric and perchloric acids on the ultraviolet spectra of the semicarbazones in 0.1 *M* semicarbazide hydrochloride. The spectra so obtained varied smoothly between the two extremes measured (8 *M* perchloric acid and 0.01 *M* hydrochloric acid), yielding titration curves

from which the pK'_a values of the conjugate acids of the semicarbazones were derived, using the H_0 values of Paul and Long.⁹ The spectral shift produced by strong acid was shown to be fully reversible by neutralization of a solution of benzaldehyde semicarbazone in 5 *M* perchloric acid. Comparison of the spectra of protonated semicarbazones in 0.1 *M* semicarbazide hydrochloride with those of the respective aldehydes in strong acid showed that no significant hydrolysis of the aldehyde had occurred under the experimental conditions.

The effect of strong acid on the over-all equilibrium for benzaldehyde semicarbazone formation in aqueous solution was determined by measuring the spectrum of benzaldehyde in various concentrations of semicarbazone at each of a number of H_0 values⁹ in hydrochloric and perchloric acid solutions. Spectra were measured for at least two intermediate semicarbazide concentrations at each acidity and compared with spectra in the absence of semicarbazide and in the presence of 0.50 *M* semicarbazide hydrochloride, in which conversion to semicarbazone or its conjugate acid is complete at all acidities. The apparent equilibrium constants for semicarbazone formation at each acidity were obtained from the absorbance at 280 μ , as described above, except that total concentrations of the reactants, rather than the free base concentrations, are used.

Results

Rate and equilibrium constants for semicarbazone formation are summarized in Table I, including a few values previously reported for the equilibrium constant for semicarbazide addition compound formation and several redetermined values of the rate constants for dehydration. At the foot of each column is the value of Hammett's ρ , calculated by the method of least squares from values obtained for the *p*-substituted benzaldehydes. The points for *p*-methoxy- and *p*-hydroxybenzaldehydes show negative deviations in the σ - ρ plots for K_1 , K_{eq} and k_{ov} , which are magnified in plots using σ -values¹⁰; this is consistent with a considerable degree of resonance stabilization of the starting benzaldehydes by these *p*-substituents.

The over-all rate of semicarbazone formation at neutrality is considerably higher for the *o*- than for the *p*-substituted benzaldehyde for every substituent except nitro. In each case, most strikingly

(9) M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

(10) R. W. Taft, Jr., S. Ehrenson, I. C. Lewis and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5352 (1959).

for the methoxy substituents, the *o*-substituted isomer reacts as fast or faster than benzaldehyde itself, while the *p*-isomer reacts more slowly.

Rate constants were also determined for the over-all reaction of hydroxylamine with *o*- and *p*-methoxybenzaldehyde. The over-all third-order rate constants for dilute solutions in 25% ethanol at ionic strength 0.32 for the acid-catalyzed reaction, determined at five apparent *pH* values between *pH* 4 and 7, were found to be $40 \times 10^7 \text{ l.}^2\text{mole}^{-2} \text{ min.}^{-1}$ for *o*-methoxybenzaldehyde and $4.8 \times 10^7 \text{ l.}^2\text{mole}^{-2}\text{min.}^{-1}$ for *p*-methoxybenzaldehyde. In one experiment carried out with 0.01 *M* hydroxylamine hydrochloride in 25% ethanol at ionic strength 0.32 (apparent *pH* 4.17), the observed rates of oxime formation for *o*- and *p*-methoxybenzaldehydes were 3.5 and 0.35 min.^{-1} , respectively; the corresponding observed rate constants in 100% ethanol containing 0.01 *M* hydroxylamine hydrochloride were 3.1 and 0.30 min.^{-1} , respectively, showing that there is no significant change in rate ratio with this change in solvent.

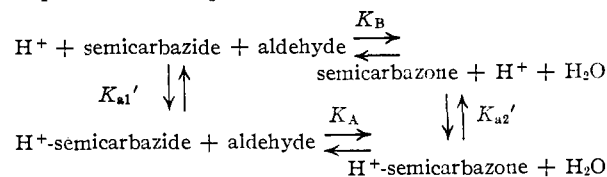
The resultant methoxy *ortho:para* rate ratios of 8.2 for oxime formation and 11.2 for semicarbazone formation compare with an *ortho:para* rate ratio of 11.0 obtained by Bloch-Chaudé for methoxybenzaldehyde Schiff base formation with *p*-toluidine.⁴ The *ortho:para* rate ratio of the hydroxybenzaldehydes for semicarbazone formation is 2.2; corresponding values reported for other reactions are 4.7 for Schiff base formation with *p*-toluidine,⁴ and 7.2 for oxime formation from hydroxylamine hydrochloride in 95% methanol.³

Rate constants for the over-all reaction in dilute solution at neutrality are the product of the equilibrium constant for semicarbazide addition, K_1 , and the rate constant for acid-catalyzed dehydration of the addition compound, $k_{2\text{H}^+}$. Rate constants for dehydration are in each case similar for *o*- and *p*-substituents, so that *ortho:para* differences in over-all rate chiefly reflect differences in the addition equilibrium. For the one case in which the *ortho:para* rate ratio for the acid-catalyzed addition exceeds two (the methoxy substituent), the rate ratio for the base-catalyzed dehydration is also high. Equilibrium constants for the over-all reaction may similarly be divided into the equilibrium constant for addition, K_1 , and the equilibrium constant for dehydration of the addition compound, K_2 , and it is again found that the *ortho* effect in each case mainly reflects differences in the equilibrium constants for the addition step.

In Table II are summarized the pK_a' values ob-

upon protonation in strong acid. The pK_a' values fall near -1.1 and are virtually independent of the substituent, suggesting that protonation occurs at the terminal carboxamide group.

A pK_a' value of $+0.95$ was estimated for the conjugate acid of benzaldehyde semicarbazone by Conant and Bartlett from the variation with acidity of the over-all equilibrium constant for benzaldehyde semicarbazone formation; the measurements, however, were not carried into a range of acidity in which a large fraction of the semicarbazone was converted to the conjugate acid.¹¹ The usefulness of the Conant and Bartlett relationship which depends on the equilibria



where

$$K_B = \frac{[\text{semicarbazone}]}{[\text{ald}][\text{semicarbazide}]} \text{ and } K_A = \frac{[\text{H}^+\text{-semicarbazone}]}{[\text{ald}][\text{H}^+\text{-semicarbazide}]}$$

was established by measuring the variation of the apparent over-all equilibrium constant for benzaldehyde semicarbazone formation, $K_0 = [\text{total semicarbazone}]/[\text{ald}][\text{total semicarbazide}]$, with increasing concentrations of strong acids. A plot of $1/K_0$ against H_0 in hydrochloric and perchloric acid solutions is shown in Fig. 2, together with a theo-

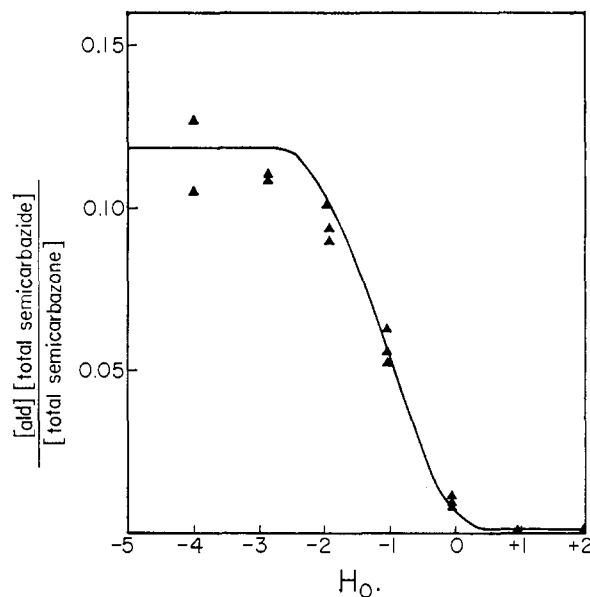


Fig. 2.—Apparent equilibrium constant for benzaldehyde semicarbazone hydrolysis ($1/K_0$) in aqueous acid at 25°; ionic strength maintained at 0.6 with KCl at $H_0 = 1$ and 2.

retical curve calculated from the independently measured values for K_{a1}' and K_{a2}' and a value for K_B (in water) of 4.5×10^5 . The inflection point in the sigmoid curve falls at $H_0 = -1.09$, which

(11) J. B. Conant and P. D. Bartlett, *ibid.*, 54, 2881 (1932), and P. D. Bartlett, Ph.D. thesis (Harvard University, 1932).

TABLE II

pK_a' VALUES OF THE CONJUGATE ACIDS OF SUBSTITUTED BENZALDEHYDE SEMICARBAZONES

Substituent	pK_a'	Wave length, $m\mu$	Substituent	pK_a'	Wave length, $m\mu$
H	-1.05	280	<i>o</i> -OH	-1.30	360
<i>o</i> -MeO	-1.15	360	<i>p</i> -Cl	-1.15	282
<i>p</i> -Meo	-1.20	360	<i>o</i> -NO ₂	-1.20	260

tained for the conjugate acids of several substituted benzaldehyde semicarbazones for which readily measurable changes in ultraviolet absorption occur

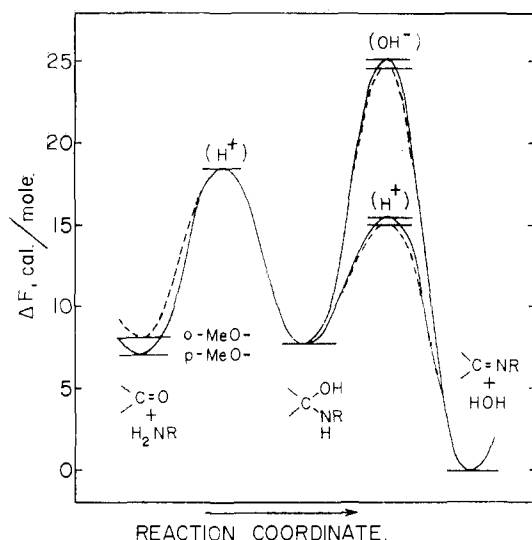


Fig. 3.—Free energy diagram for methoxybenzaldehyde semicarbazone formation: solid line, *p*-methoxybenzaldehyde; dashed line, *o*-methoxybenzaldehyde. H^+ and OH^- refer to acid-catalyzed and base-catalyzed steps of the reaction, respectively. The second step becomes rate-determining at neutral and alkaline pH because of the existence of an uncatalyzed first step (not shown).

agrees well with the spectrophotometrically determined pK' value of benzaldehyde semicarbazone of -1.05 .

Discussion

Ortho:para ratios for the equilibrium constants for semicarbazide addition compound formation from substituted benzaldehydes fall in the series $MeO > HO \sim Cl > Me > H (= 1) > NO_2$. Similar ratios are found for the rate and equilibrium constants of the over-all reaction. *Ortho* effects on the rate constants for acid- and base-catalyzed dehydration are small. The *ortho* effects on the over-all rates of oxime and of semicarbazone formation are considerably smaller than those originally reported by Vavon and Montheard under somewhat different conditions,² but are similar to those reported by others for reactions of hydroxylamine³ and *p*-toluidine⁴ with substituted benzaldehydes. The reason for these differences is not known, but may be related to the requirement for strict pH control in studies of the rates of these pH -sensitive reactions.¹²

High methoxy *ortho:para* rate ratios are characteristic of a wide variety of nucleophilic reactions with substituted aromatic compounds. Ratios in excess of one (which is, by definition, the *ortho:para* ratio for hydrogen) have been found for the methoxy substituent in methyl benzoate¹³ and cyclohexyl benzoate¹⁴ formation, saponification of ethyl benzoates¹⁵ (for ethoxy), alkaline hydrolysis

(12) D. C. Knorre and N. M. Emanuel, *Uspekhi Khim.*, **24**, 275 (1955).

(13) R. J. Hartman and A. G. Gassman, *J. Am. Chem. Soc.*, **62**, 1559 (1940).

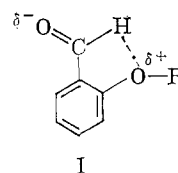
(14) R. J. Hartman, H. M. Hoogsteen and J. A. Moede, *ibid.*, **66**, 1714 (1944).

(15) (a) E. Tommila, L. Brehmer and H. Elo, *Ann. Acad. Sci. Fennicae*, **A57**, No. 9, 3 (1941) (*C. A.*, **38**, 6173 (1944)), (b) E. Tommila, *ibid.*, **A57**, No. 13, 3 (1941) (*C. A.*, **38**, 6171 (1944)).

of benzamides,¹⁶ benzoyl chloride ethanolysis,¹⁷ aryl sulfate hydrolysis,¹⁸ and reduction of thio-benzophenones by reduced diphosphopyridine nucleotide.¹⁹ Furthermore, the equilibrium constants for cyanohydrin formation are increased by a variety of *o*-substituents²⁰ and 2-methoxyisophthalate monoethyl ester undergoes saponification faster than the corresponding unsubstituted compound.²¹

The effect of an *ortho*, compared to a *para*, methoxy group on the various steps of semicarbazone formation might be regarded as a stabilization by the *o*-substituent of the transition states for the addition step and the over-all reaction, as well as of the addition compound intermediate and the final product, all relative to the starting material. However, the results are most simply accounted for in terms of a destabilization of the starting *o*-methoxybenzaldehyde, relative to the *p*-isomer. The complete free energy diagrams for the various steps of the reaction are shown in Fig. 3, and it is evident that the observed rate and equilibrium effects may be in large part accounted for by such a destabilization of the *o*-substituted starting material. It is now necessary to account for such a destabilization.

It has been suggested that hydrogen bonding may occur between formyl hydrogen and electron-rich *o*-substituents^{2,22-24} and that such hydrogen-



bonding may facilitate reactions of substituted benzaldehydes with nitrogen bases.² Such hydrogen bonding would be expected to withdraw positive charge from the carbonyl group and stabilize the starting material; it would, therefore, decrease susceptibility to nucleophilic attack. In any case, such hydrogen bonding clearly cannot account for the observed effects on the several individual rate and equilibrium constants of semicarbazone formation. Furthermore, the rate acceleration observed with *o*-methyl substitution cannot be accounted for by such hydrogen bonding, because the methyl group has no available free electron pair.

The reactivity of an *o*-substituted benzene compound may exceed that of the *p*-substituted isomer in a reaction sensitive to inductive effects if the *o*-substituent exerts a larger inductive effect than the *p*-substituent. However, the over-all rate of semicarbazone formation is not sensitive to induc-

(16) E. Reid, *Am. Chem. J.*, **24**, 397 (1900).

(17) J. F. Norris, E. V. Fasce and C. J. Staud, *J. Am. Chem. Soc.*, **57**, 1415 (1935).

(18) G. N. Burckhardt, W. G. K. Ford and E. Singleton, *J. Chem. Soc.*, 17 (1936).

(19) R. H. Abeles, R. F. Hutton and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957).

(20) A. Lapworth and R. H. F. Manske, *J. Chem. Soc.*, 2533 (1928).

(21) C. A. Burkhard and R. E. Burnett, *J. Org. Chem.*, **25**, 1065 (1960).

(22) S. Pinchas, *Chemistry & Industry*, 1451 (1959).

(23) G. Vavon and J. Scandel, *Compt. rend.*, **223**, 1144 (1946).

(24) B. C. Curran, *J. Am. Chem. Soc.*, **67**, 1835 (1945).

tive effects ($\rho = 0.07$), yet gives a methoxy *ortho*:*para* ratio of 11.2. High ratios are found for every other substituent except nitro. Other reactions with very low ρ -values and high *ortho*:*para* ratios are acid-catalyzed methyl benzoate formation¹³ and cyclohexyl benzoate formation.¹⁴ On the other hand, k_2 , the rate constant of the dehydration reaction, is sensitive to inductive effects ($\rho = -1.7$), yet *ortho*:*para* rate differences are small; the most marked difference of twofold for methoxy applies to the acid- and base-catalyzed dehydrations equally, and is thus independent of ρ . Other examples of reactions with high reaction constants and small *ortho*:*para* differences include the basic methanolysis of menthyl benzoates²⁵ and the alkaline hydrolysis of benzamides.¹⁶ The results, therefore, cannot be accounted for by differences in inductive effects between *o*- and *p*-substituents.

Rate and equilibrium constants for semicarbazone formation could be increased by *o*-substituents through steric effects if the transition states and products were less sterically hindered than the starting materials. This is not the case since (i) on chemical grounds no such relationship would be expected to exist for all of the rate and equilibrium constants which show a high *ortho*:*para* ratio and (ii) the effect of increasing size of *o*-substituents is to decrease *ortho*:*para* rate and equilibrium constant ratios, indicating that these steps are hindered, rather than favored, by large *o*-substituents (Table I). Steric effects of the hydroxy and methoxy groups should, in any case, be smaller than the steric effect of the *o*-methyl group, which itself has little or no steric effect in benzaldehydes and benzaldehyde semicarbazones, according to molecular models, spectral studies and dipole moment data.²⁶ The difficulty of accounting in this way for the reactivity of *o*-substituted benzene derivatives in other reactions is illustrated by the fact that if hydrogen is included in Taft's series of E_s values, which has been suggested as a measure of the steric effects of *o*-substituents,²⁷ it falls between the large substituents on the one hand and the ethoxy and methoxy groups on the other, although hydrogen is considered the smallest of substituents.²⁸ It must be concluded either that alkoxy substituents are less bulky than hydrogen or that the E_s scale for aromatic substituents cannot realistically be extended to alkoxy substituents as a measure of steric effects alone.

There does not appear to be any correlation between the rate and equilibrium effects on the various steps and the mutual polarizability of the reactants, which might lead to a rate enhancement due to London force interaction.²⁹ Similarly, the results do not appear to be readily explicable in terms of substituent field effects³⁰ in the products, reactants and transition states.

(25) R. W. Taft, Jr., M. S. Newman and F. H. Verhoek, *J. Am. Chem. Soc.*, **72**, 4511 (1950).

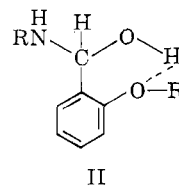
(26) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955), J. W. Smith, *ibid.*, 109 (1953).

(27) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 2729, 3120 (1952).

(28) Based on the data from the series of *o*-substituted benzoate reactions used by Taft for the calculation of E_s values for other *o*-substituents.²⁷

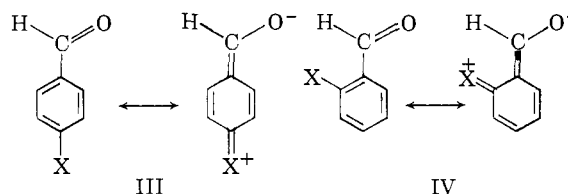
(29) J. D. Reinheimer and J. F. Bunnett, *J. Am. Chem. Soc.*, **81**, 815 (1959).

Our original expectation was that the rapid reactions of *o*-substituted methoxy- and hydroxybenzaldehydes might be due to stabilization of the addition intermediate by hydrogen bonding as in II. There is strong evidence that hydrogen bonding



of this kind occurs in *o*-methoxybenzoic acid in non-polar solvents.³¹ Such hydrogen bonding clearly does not account for the results reported here in predominantly aqueous solution, however, since the over-all equilibrium constant for semicarbazone formation is also favored by *o*-substituents.

We conclude that the observed increase in the reactivity of certain *o*-substituted benzaldehydes constitutes strong evidence that electron donation by resonance is more effective from the *p*- than from the *o*-position. *p*-Methoxy-, -hydroxy- and -chlorobenzaldehydes (III) will therefore be stabilized relative to the corresponding *o*-substituted compounds (IV); this will increase both the rate and the equilibrium constants for reactions of the *o*-isomer.



Such resonance stabilization is expected to be less important for the —C=N— group in the product than for the highly polar —C=O group of the starting material, with its strongly electronegative oxygen atom.³² If the relatively small rate and equilibrium constant differences between *o*- and *p*-methylbenzaldehydes reflect a significant difference in stabilization of the two isomers, they may be taken as evidence for hyperconjugation from the *p*-position. The high *ortho*:*para* ratios found for electrophilic substitution of aromatic compounds with substituents which are electron-withdrawing by resonance constitute strong evidence that *p*-quinoid structures are intrinsically

(30) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., Methuen and Co., Ltd., London, 1958, p. 400, and references therein.

(31) (a) M. M. Davis and H. B. Hetzer, *J. Research U. S. Bur. Standards*, **60**, 569 (1958); (b) J. J. Fox and A. E. Martin, *Nature*, **143**, 199 (1939); (c) M. Davies and D. M. L. Griffiths, *J. Chem. Soc.*, 132 (1955).

(32) A. W. Baker and A. T. Shulgin (*J. Am. Chem. Soc.*, **81**, 1523 (1959)) have concluded, from a study of the effects of substituents on intramolecular hydrogen bonding in a series of *o*-hydroxyaromatic Schiff bases in carbon tetrachloride that there is little difference between the polar effects of *o*- and *p*-substituents and that the small differences which are observed suggest that both resonance and inductive effects are stronger in the *o*-position. This difference, if significant, is not at variance with our conclusion, since differences in charge separation would strongly favor *ortho* over *para* resonance forms in such a non-polar solvent as carbon tetrachloride. M. Charton has recently summarized other data suggesting that the electrical effects of *o*- and *p*-substituents are similar (*Can. J. Chem.*, **38**, 2493 (1960)).

